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(54) Title: NOVEL GENES, COMPOSITIONS, KITS, AND METHODS FOR IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF CERVICAL CANCER

(57) Abstract: The invention relates to newly discovered nucleic acid molecules and proteins associated with cervical cancer including pre-malignant conditions such as dysplasia. Compositions, kits, and methods for detecting, characterizing, preventing, and treating human cervical cancers are provided.

WO 02/101075 A2

NOVEL GENES, COMPOSITIONS, KITS, AND METHODS FOR
IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF
CERVICAL CANCER

5 RELATED APPLICATIONS

The present application claims priority to U.S. provisional patent application serial no. 60/298,159, filed on June 13, 2001, U.S. provisional patent application serial no. 60/298,155, filed on June 13, 2001, and U.S. provisional patent application serial no. 60/335,936, filed on November 14, 2001, all of which are expressly incorporated by
10 reference.

FIELD OF THE INVENTION

The field of the invention is cervical cancer, including diagnosis, characterization, management, and therapy of cervical cancer.

15

BACKGROUND OF THE INVENTION

The increased number of cancer cases reported in the United States, and, indeed, around the world, is a major concern. Currently there are only a handful of treatments available for specific types of cancer, and these provide no absolute guarantee
20 of success. In order to be most effective, these treatments require not only an early detection of the malignancy, but a reliable assessment of the severity of the malignancy.

Cancer of the cervix is one of the most common malignancies in women and remains a significant public health problem throughout the world. In the United States alone, invasive cervical cancer accounts for approximately 19% of all
25 gynecological cancers. In 1996, it was estimated that there were 14,700 newly diagnosed cases and 4900 deaths attributed to this disease (American Cancer Society, Cancer Facts & Figures 1996, Atlanta, Ga.: American Cancer Society, 1996). In many developing countries, where mass screening programs are not widely available, the clinical problem is more serious. Worldwide, the number of new cases is estimated to be 471,000 with a
30 four-year survival rate of only 40% (Munoz et al., 1989, *Epidemiology of Cervical Cancer* In: "Human Papillomavirus", New York, Oxford Press, pp 9-39; National Institutes of Health, Consensus Development Conference Statement on Cervical Cancer, Apr.1-3, 1996).

The precursor to cervical cancer is dysplasia, also known in the art as cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SIL). While it is not understood how normal cells become transformed, the concept of a continuous spectrum of histopathological change from normal, stratified epithelium through CIN to
5 invasive cancer has been widely accepted for many years. A large body of epidemiological and molecular biological evidence has established human papillomavirus (HPV) infection as a causative factor in cervical cancer. HPV is found in 85% or more of squamous cell invasive lesions, which represent the most common histologic type seen in cervical carcinoma. Additional cofactors have also been
10 identified, including oncogenes that have been activated by point mutations and chromosomal translocations or deletions.

In light of this, cervical cancer remains a highly preventable form of cancer when pre-invasive lesions are detected early. Cytological examination of Papanicolaou-stained cervical smears (also referred to as Pap smears) is currently the
15 principle method for detecting cervical cancer. Not surprisingly, the effectiveness of Pap smear screening varies depending not only upon the quality of the sample being used, but also upon subjective parameters that are inherent to the analysis. In addition, despite the historical success of the test, concerns have arisen regarding its ability to reliably predict the behavior of some pre-invasive lesions (Ostor *et al.*, 1993, *Int. J. Gynecol.*
20 *Pathol.* 12: 186-192; and Genest *et al.*, 1993, *Human Pathol.* 24: 730-736).

SUMMARY OF THE INVENTION

The invention relates to cancer markers (hereinafter "markers" or "markers of the inventions"), which are listed in Table 1. The invention provides
25 nucleic acids and proteins that are encoded by or correspond to the markers (hereinafter "marker nucleic acids" and "marker proteins," respectively). Table 1 provides the sequence identifiers of the sequences of such marker nucleic acids and proteins listed in the accompanying Sequence Listing. The invention further provides antibodies, antibody derivatives and antibody fragments which bind specifically with such proteins
30 and/or fragments of the proteins.

The invention also relates to various methods, reagents and kits for diagnosing, staging, prognosing, monitoring and treating cervical cancer. "Cervical cancer" as used herein includes carcinomas, (*e.g.*, carcinoma in situ, invasive

carcinoma, metastatic carcinoma) and pre-malignant conditions, (*e.g.*, dysplasia, including CIN or SIL). In one embodiment, the invention provides a diagnostic method of assessing whether a patient has cervical cancer or has higher than normal risk for developing cervical cancer, comprising the steps of comparing the level of expression of
5 a marker of the invention in a patient sample and the normal level of expression of the marker in a control, *e.g.*, a sample from a patient without cervical cancer. A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with cervical cancer or has higher than normal risk for developing cervical cancer.

10 According to the invention, the markers are selected such that the positive predictive value of the methods of the invention is at least about 10%, preferably about 25%, more preferably about 50% and most preferably about 90%. Also preferred for use in the methods of the invention are markers that are differentially expressed, as compared to normal cervical cells, by at least two-fold in at least about 20%, more
15 preferably about 50% and most preferably about 75% of any of the following conditions: stage 0 cervical cancer patients, stage I cervical cancer patients, stage II cervical cancer patients, stage III cervical cancer patients, stage IV cervical cancer patients, grade I cervical cancer patients, grade II cervical cancer patients, grade III cervical cancer patients, squamous cell (epidermoid) cervical cancer patients, cervical adenocarcinoma
20 patients, cervical adenosquamous carcinoma patients, small-cell cervical carcinoma patients, malignant cervical cancer patients, patients with primary carcinomas of the cervix, patients with primary malignant lymphomas of the cervix and patients with secondary malignant lymphomas of the cervix, and all other types of cancers, malignancies and transformations associated with the cervix.

25 In a preferred diagnostic method of assessing whether a patient is afflicted with cervical cancer (*e.g.*, new detection ("screening"), detection of recurrence, reflex testing), the method comprises comparing:

- a) the level of expression of a marker of the invention in a patient sample,
and
- 30 b) the normal level of expression of the marker in a control non-cervical cancer sample.

A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with cervical cancer.

The invention also provides diagnostic methods for assessing the efficacy of a therapy for inhibiting cervical cancer in a patient. Such methods comprise comparing:

- a) expression of a marker of the invention in a first sample obtained from the patient prior to providing at least a portion of the therapy to the patient, and
- 10 b) expression of the marker in a second sample obtained from the patient following provision of the portion of the therapy.

A significantly lower level of expression of the marker in the second sample relative to that in the first sample is an indication that the therapy is efficacious for inhibiting cervical cancer in the patient.

15 It will be appreciated that in these methods the "therapy" may be any therapy for treating cervical cancer including, but not limited to, chemotherapy, radiation therapy, surgical removal of tumor tissue, gene therapy and biologic therapy such as the administering of antibodies and chemokines. Thus, the methods of the invention may be used to evaluate a patient before, during and after therapy, for
20 example, to evaluate the reduction in tumor burden.

In a preferred embodiment, the diagnostic methods are directed to therapy using a chemical or biologic agent. These methods comprise comparing:

- a) expression of a marker of the invention in a first sample obtained from the patient and maintained in the presence of the chemical or biologic
25 agent, and
- b) expression of the marker in a second sample obtained from the patient and maintained in the absence of the agent.

A significantly lower level of expression of the marker in the second sample relative to that in the first sample is an indication that the agent is efficacious for inhibiting cervical
30 cancer, in the patient. In one embodiment, the first and second samples can be portions of a single sample obtained from the patient or portions of pooled samples obtained from the patient.

The invention additionally provides a monitoring method for assessing the progression of cervical cancer in a patient, the method comprising:

- a) detecting in a patient sample at a first time point, the expression of a marker of the invention;
- 5 b) repeating step a) at a subsequent time point in time; and
- c) comparing the level of expression detected in steps a) and b), and therefrom monitoring the progression of cervical cancer in the patient.

A significantly higher level of expression of the marker in the sample at the subsequent time point from that of the sample at the first time point is an indication that the cervical
10 cancer has progressed, whereas a significantly lower level of expression is an indication that the cervical cancer has regressed.

The invention further provides a diagnostic method for determining whether cervical cancer has metastasized or is likely to metastasize in the future, the method comprising comparing:

- 15 a) the level of expression of a marker of the invention in a patient sample, and
- b) the normal level (or non-metastatic level) of expression of the marker in a control sample.

A significantly higher level of expression in the patient sample as compared to the
20 normal level (or non-metastatic level) is an indication that the cervical cancer has metastasized or is likely to metastasize in the future.

The invention moreover provides a test method for selecting a composition for inhibiting cervical cancer in a patient. This method comprises the steps of:

- 25 a) obtaining a sample comprising cancer cells from the patient;
- b) separately maintaining aliquots of the sample in the presence of a plurality of test compositions;
- c) comparing expression of a marker of the invention in each of the aliquots; and
- 30 d) selecting one of the test compositions which significantly reduces the level of expression of the marker in the aliquot containing that test composition, relative to the levels of expression of the marker in the presence of the other test compositions.

The invention additionally provides a test method of assessing the cervical carcinogenic potential of a compound. This method comprises the steps of:

- a) maintaining separate aliquots of cervical cells in the presence and absence of the compound; and
- 5 b) comparing expression of a marker of the invention in each of the aliquots.

A significantly higher level of expression of the marker in the aliquot maintained in the presence of the compound, relative to that of the aliquot maintained in the absence of the compound, is an indication that the compound possesses cervical carcinogenic potential.

10 In addition, the invention further provides a method of inhibiting cervical cancer in a patient. This method comprises the steps of:

- a) obtaining a sample comprising cancer cells from the patient;
- b) separately maintaining aliquots of the sample in the presence of a plurality of compositions;
- 15 c) comparing expression of a marker of the invention in each of the aliquots; and
- d) administering to the patient at least one of the compositions which significantly lowers the level of expression of the marker in the aliquot containing that composition, relative to the levels of expression of the marker in the presence of the other compositions.

20 In the aforementioned methods, the samples or patient samples comprise cells obtained from the patient. The cells may be found in a cervical smear collected, for example, by a cervical brush. In another embodiment, the sample is a body fluid. Such fluids include, for example, blood fluids, lymph, ascitic fluids, gynecological fluids, urine, and fluids collected by vaginal rinsing. In a further embodiment, the patient sample is *in vivo*.

According to the invention, the level of expression of a marker of the invention in a sample can be assessed, for example, by detecting the presence in the sample of:

- 30 • the corresponding marker protein (*e.g.*, a protein having one of the sequences set forth as "SEQ ID NO (AAs)" in Table 1, or a fragment of the protein (*e.g.* by using a reagent, such as an antibody, an antibody derivative,

an antibody fragment or single-chain antibody, which binds specifically with the protein or protein fragment)

- the corresponding marker nucleic acid (*e.g.* a nucleotide transcript having one of the nucleic acid sequences set forth as "SEQ ID NO (nts)" in Table 1, or a complement thereof), or a fragment of the nucleic acid (*e.g.* by contacting transcribed polynucleotides obtained from the sample with a substrate having affixed thereto one or more nucleic acids having the entire or a segment of the nucleic acid sequence of any of the SEQ ID NO (nts), or a complement thereof)
- a metabolite which is produced directly (*i.e.*, catalyzed) or indirectly by the corresponding marker protein.

According to the invention, any of the aforementioned methods may be performed using a plurality (*e.g.* 2, 3, 5, or 10 or more) of cervical cancer markers, including cervical cancer markers known in the art. In such methods, the level of expression in the sample of each of a plurality of markers, at least one of which is a marker of the invention, is compared with the normal level of expression of each of the plurality of markers in samples of the same type obtained from control humans not afflicted with cervical cancer. A significantly altered (*i.e.*, increased or decreased as specified in the above-described methods using a single marker) level of expression in the sample of one or more markers of the invention, or some combination thereof, relative to that marker's corresponding normal or control level, is an indication that the patient is afflicted with cervical cancer. For all of the aforementioned methods, the marker(s) are preferably selected such that the positive predictive value of the method is at least about 10%.

In a further aspect, the invention provides an antibody, an antibody derivative, or an antibody fragment, which binds specifically with a marker protein (*e.g.*, a protein having one of the amino acid sequences set forth in the Sequence Listing) or a fragment of the protein. The invention also provides methods for making such antibody, antibody derivative, and antibody fragment. Such methods may comprise immunizing a mammal with a protein or peptide comprising the entirety, or a segment of 10 or more amino acids, of a marker protein (*e.g.*, a protein having one of the amino acid sequences set forth in the Sequence Listing), wherein the protein or peptide may be obtained from a cell or by chemical synthesis. The methods of the invention also encompass producing

monoclonal and single-chain antibodies, which would further comprise isolating splenocytes from the immunized mammal, fusing the isolated splenocytes with an immortalized cell line to form hybridomas, and screening individual hybridomas for those that produce an antibody that binds specifically with a marker protein or a
5 fragment of the protein.

In another aspect, the invention relates to various diagnostic and test kits. In one embodiment, the invention provides a kit for assessing whether a patient is afflicted with cervical cancer. The kit comprises a reagent for assessing expression of a marker of the invention. In another embodiment, the invention provides a kit for
10 assessing the suitability of a chemical or biologic agent for inhibiting cervical cancer in a patient. Such a kit comprises a reagent for assessing expression of a marker of the invention, and may also comprise one or more of such agents. In a further embodiment, the invention provides kits for assessing the presence of cervical cancer cells or treating cervical cancers. Such kits comprise an antibody, an antibody derivative, or an antibody
15 fragment, which binds specifically with a marker protein, or a fragment of the protein. Such kits may also comprise a plurality of antibodies, antibody derivatives, or antibody fragments wherein the plurality of such antibody agents binds specifically with a marker protein, or a fragment of the protein.

In an additional embodiment, the invention also provides a kit for
20 assessing the presence of cervical cancer cells, wherein the kit comprises a nucleic acid probe that binds specifically with a marker nucleic acid or a fragment of the nucleic acid. The kit may also comprise a plurality of probes, wherein each of the probes binds specifically with a marker nucleic acid, or a fragment of the nucleic acid.

In a further aspect, the invention relates to methods for treating a patient
25 afflicted with cervical cancer or at risk of developing cervical cancer. Such methods may comprise reducing the expression and/or interfering with the biological function of a marker of the invention. In one embodiment, the method comprises providing to the patient an antisense oligonucleotide or polynucleotide complementary to a marker nucleic acid, or a segment thereof. For example, an antisense polynucleotide may be
30 provided to the patient through the delivery of a vector that expresses an anti-sense polynucleotide of a marker nucleic acid or a fragment thereof. In another embodiment, the method comprises providing to the patient an antibody, an antibody derivative, or antibody fragment, which binds specifically with a marker protein or a fragment of the

protein. In a preferred embodiment, the antibody, antibody derivative or antibody fragment binds specifically with a protein having one of the amino acid sequences set forth in the Sequence Listing, or a fragment of the protein.

It will be appreciated that the methods and kits of the present invention
5 may also include known cancer markers including known cervical cancer markers. It will further be appreciated that the methods and kits may be used to identify cancers other than cervical cancer.

DETAILED DESCRIPTION OF THE INVENTION

10 The invention relates to newly discovered cancer markers associated with the cancerous state of cervical cells. It has been discovered that the higher than normal level of expression of any of these markers or combination of these markers correlates with the presence of cervical cancer including pre-malignant conditions such as dysplasia, in a patient. Methods are provided for detecting the presence of cervical
15 cancer in a sample, the absence of cervical cancer in a sample, the stage of a cervical cancer, and other characteristics of cervical cancer that are relevant to prevention, diagnosis, characterization, and therapy of cervical cancer in a patient. Methods of treating cervical cancer are also provided.

Table 1 lists the markers of the invention which are over-expressed in
20 cervical cancer cells compared to normal (*i.e.*, non-cancerous) cervical cells and comprises markers listed in Tables 2 and 3. Table 2 lists newly-identified nucleotide and amino acid sequences. Table 3 lists newly-identified nucleotide sequences. Tables 1-3 provide the sequence listing identifiers of the cDNA sequence of a nucleotide transcript and the amino acid sequence of a protein encoded by or corresponding to each
25 marker, as well as the location of the protein coding sequence within the cDNA sequence.

Table 1

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
M661	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 1	1	2	223..11946
M662	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 2	3	4	223..11922
M663	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 3	5	6	223..12000
M664	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 4	7	8	223..11976
M1	APOL1: Apolipoprotein L-I mRNA, splice variant A, major form	9	10	213..1364
M2	APOL1: Apolipoprotein L-I mRNA, splice variant B, minor form	11	12	274..1518
M3	APOL3: apolipoprotein L, 3; TNF-inducible protein CG12-1	13	14	418..1413
OV3	AQP5: Aquaporin 5	15	16	519..1316
M4	BC001980: clone MGC:5618	17	18	157..225
M5	BST2: Bone marrow stromal cell antigen 2	19	20	10..552
M6	BTEB1: basic transcription element binding protein 1	21	22	1265..1999
M665	CD74: CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated)	23	24	8..706
M7	CDC20: CDC20 cell cycle protein	25	26	45..1544
M8	CDKN2C: cyclin-dependent kinase inhibitor 2C, p18	27	28	1216..1722
M9	CKTSF1B1: (cysteine knot superfamily 1, BMP antagonist 1), gremlin	29	30	45..1544
M10	CLDN1: claudin 1	31	32	221..856
M11	CLIC4: chloride intracellular channel 4	33	34	198..959
M12	COL1A1: collagen, type I, alpha 1	35	36	120..4514
M13	COL1A2: collagen, type I, alpha 2	37	38	140..4240
M14	COL8A1: collagen, type VIII, alpha 1	39	40	1..2235
M15	COPA: coatomer protein complex, subunit alpha	41	42	467..4141
M16	CRIP1: cysteine-rich protein 1 (intestinal)	43	44	1..234
M17	CTGF: connective tissue growth factor	45	46	146..1195
M18	DOC: downregulated in ovarian cancer 1	47	48	135..2393
M19	EFNA1: ephrin-A1	49	50	74..691
M481	EPPK1: epiplakin 1	51	52	89..15286
M20	FLJ11350: hypothetical protein FLJ11350	53	54	106..1047
M21	FLJ13809: hypothetical protein FLJ13809	55	56	64..1593
M22	FLJ20500: hypothetical protein FLJ20500	57	58	198..896
M23	FLJ23399: hypothetical protein FLJ23399	59	60	283..1770
M24	FN1: Fibronectin 1, variant 1	61	62	<1..2384
M25	FN1: Fibronectin 1, variant 2	63	64	<1..6988
M482	FOSL2: FOS-like antigen 2, variant 1	65	66	324..1304
M483	FOSL2: FOS-like antigen 2, variant 2	67	66	324..1304
M484	FSHPRH1: FSH primary response (LRPR1, rat) homolog 1	68	69	270..2540
M26	FY: Duffy blood group	70	71	495..1511

M485	G1P3:interferon, alpha-inducible protein (clone IFI-6-16)	72	73	108..500
M486	GW112: GW112 protein	74	75	509..1072
M27	HSKERUV: clone 266, Human radiated keratinocyte mRNA 266 (keratin-related protein)	76	77	<1..801
M28	HSPC121: butyrate-induced transcript 1	78	79	150..1271
M29	HUMCLPB: Coactosin like protein	80	81	150..576
M487	hypothetical protein	82	83	58..8163
M30	IFI27: (interferon, alpha-inducible protein 27	84	85	55..423
OV31	IFI30: interferon, gamma-inducible protein 30	86	87	41..952
M31	IFITM2: interferon induced transmembrane protein 2 (1-8D)	88	89	280..678
M32	IGFBP-3: insulin-like growth factor binding protein 3	90	91	133..1009
M33	IL8RA: interleukin 8	92	93	75..374
M34	INHBA: Inhibin, beta-1	94	95	86..1366
M488	ITGA3: integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor), variant a	96	97	74..3229
M454	ITGA3: integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor), variant b	98	99	74..3274
M35	ITGB6: integrin, beta 6	100	101	195..2561
M36	KATI1: L-kynurenine/alpha-aminoadipate aminotransferase	102	103	454..1731
M666	KCNAB1: potassium voltage-gated channel, shaker-related subfamily, beta member 1, variant 1	104	105	89..1315
M667	KCNAB1: potassium voltage-gated channel, shaker-related subfamily, beta member 1, variant 2	106	107	54..1313
M668	KCNAB1: potassium voltage-gated channel, shaker-related subfamily, beta member 1, variant 3	108	109	28..1233
M37	KIAA0662: KIAA0662 protein	110	111	<1..2035
M38	LAMA3: Laminin, alpha-3 (nicein (150kD), (kalinin (165kD), BM600 (150kD)	112	113	1..5142
M39	LAMC2: laminin, gamma 2	114	115	90..3671
M40	LSM5: U6 snRNA-associated Sm-like protein	116	117	1..276
M41	LUM: lumican	118	119	85..1101
M42	MACMARCKS: macrophage myristoylated alanine-rich C kinase substrate	120	121	14..601
M43	MAGP: microfibrillar-associated protein 2 precursor, transcript variant 1	122	123	115..666
M44	MAGP: microfibrillar-associated protein 2 precursor, transcript variant 2	124	125	100..651
M45	MAPK: mitogen-activated protein kinase 1	126	127	328..1410
M489	MCM6: minichromosome maintenance deficient (mis5, S. pombe) 6	128	129	62..2527
M46	MDK: midkine (neurite growth-promoting factor 2)	130	131	26..457
M47	MGP: matrix Gla protein	132	133	47..358
M48	MMP12: matrix metalloproteinase 12	134	135	13..1425
M49	MMP3: matrix metalloproteinase 3, stromelysin 1, progelatinase	136	137	64..1497
M294	MMP7: matrix metalloproteinase 7 (matrilysin, uterine), PUMP1 proteinase, variant 1	138	139	48..851
OV52	MMP7: matrix metalloproteinase 7 (matrilysin, uterine), PUMP1 proteinase, variant 2	140	139	28..831

M50	MMP9: matrix metalloproteinase 9, gelatinase B, 92kD gelatinase, 92kD type IV collagenase	141	142	20..2143
OV68	MSLN: mesothelin, variant 1	143	144	88..2196
OV69	MSLN: mesothelin, variant 2	145	146	88..1980
OV70	MSLN: mesothelin, variant 3	147	148	88..1950
OV71	MSLN: mesothelin, variant 4	149	150	88..2172
OV72	MSLN: mesothelin, variant 5	151	152	88..1926
OV43	MSLN: mesothelin, variant 6	153	154	88..1956
OV45	MUC1: mucin 1, transmembrane, variant 1	155	156	58..1605
M669	MUC1: mucin 1, transmembrane, variant 2	157	158	74..3841
M51	MYBL2: v-myb avian myeloblastosis viral oncogene homolog-like 2	159	160	128..2230
M52	MYH11: smooth muscle myosin heavy chain 11, isoform SM1	161	162	89..6007
M53	MYH11: smooth muscle myosin heavy chain 11, isoform SM2	163	164	89..5905
M54	NK4: natural killer cell transcript 4, variant 1	165	166	60..764
M670	NK4: natural killer cell transcript 4, variant 2	167	168	60..764
M55	NP25: (neuronal protein)	169	170	50..898
OV48	OPN-a (osteopontin), SPP1 (secreted phosphoprotein 1), bone sialoprotein I	171	172	1..942
OV49	OPN-b (osteopontin), SPP1 (secreted phosphoprotein 1), bone sialoprotein I	173	174	88..990
OV50	OPN-c (osteopontin), SPP1 (secreted phosphoprotein 1), bone sialoprotein I	175	176	1..861
M56	OSF-2, osteoblast specific factor 2 (fascin I-like), variant 1	177	178	12..2522
M491	OSF-2, osteoblast specific factor 2 (fascin I-like), variant 2	179	180	28..2367
M57	PIM2: pim-2 oncogene	181	182	186..1190
M58	PLAU: plasminogen activator, urokinase	183	184	77..1372
M59	PLK: polo (Drosophila)-like kinase	185	186	64..1875
M671	PNN: pinin, desmosome associated protein	187	188	31..2262
M60	PRG1: proteoglycan 1, secretory granule	189	190	25..501
M61	PTH1H: parathyroid hormone-like hormone	191	192	304..831
M62	PTN: pleiotrophin (heparin binding growth factor 8, neurite growth-promoting factor 1)	193	194	1542..2048
M63	RAB6KIFL: RAB6 interacting, kinesin-like (rabkinesin6)	195	196	28..2700
M64	RARRES3: retinoic acid receptor responder (tazarotene induced) 3	197	198	62..556
M65	RBP1: retinol-binding protein 1(cellular), CRABP-I, CRBP-I	199	200	126..533
M66	RGS16: Regulator of G protein signaling-16	201	202	93..701
M67	S100A2: S100 calcium binding protein A2, variant 1	203	204	72..362
M68	S100A2: S100 calcium binding protein A2, variant 2	205	206	41..334
M69	SCYA20: small inducible cytokine subfamily A (Cys-Cys), member 20	207	208	59..349
M70	SPARC: Osteonectin (secreted protein, acidic, cysteine-rich)	209	210	58..969
M71	STCH: stress 70 protein chaperone, microsome-associated	211	212	37..1452
M492	STK12: serine/ threonine kinase 12	213	214	58..1092

M72	TK1: thymidine kinase 1, soluble	215	216	58..762
OV86	TMPRSS4: transmembrane protease, serine 4	217	218	310..1623
M73	TMSB4X: thymosin, beta 4, X chromosome	219	220	78..212
M74	TOP2A: topoisomerase (DNA) II alpha (170kD)	221	222	37..4632
M493	TPM1: tropomyosin 1 (alpha)	223	224	57..911
M75	TXN: thioredoxin	225	226	64..381
M76	UBCH10: ubiquitin carrier protein E2-C	227	228	41..580
M77	UBD: diubiquitin	229	230	19..516
M78	unnamed gene (1)	231	232	45..1353
M79	unnamed gene (2)	233	234	1..1508
M80	VATD: vacuolar proton pump delta polypeptide	235	236	166..909
M81	ZWINT: ZW10 interactor	237	238	25..858

Table 2

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
M661	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 1	1	2	223..1194 6
M662	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 2	3	4	223..1192 2
M663	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 3	5	6	223..1200 0
M664	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 4	7	8	223..1197 6
OV68	MSLN: mesothelin, variant 1	143	144	88..2196
OV69	MSLN: mesothelin, variant 2	145	146	88..1980
OV70	MSLN: mesothelin, variant 3	147	148	88..1950
OV71	MSLN: mesothelin, variant 4	149	150	88..2172
OV72	MSLN: mesothelin, variant 5	151	152	88..1926
M670	NK4: natural killer cell transcript 4, variant 2	167	168	60..764
M67	S100A2: S100 calcium binding protein A2, variant 1	203	204	72..362
OV86	TMPRSS4: transmembrane protease, serine 4	217	218	310..1623
M78	unnamed gene (1)	231	232	45..1353
M79	unnamed gene (2)	233	234	1..1508

Table 3

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
M481	EPPK1: epiplakin 1	51	52	89..15286
M482	FOSL2: FOS-like antigen 2, variant 1	65	66	324..1304
M483	FOSL2: FOS-like antigen 2, variant 2	67	66	324..1304
M484	FSHPRH1: FSH primary response (LRPR1, rat) homolog 1	68	69	270..2540
M35	ITGB6: integrin, beta 6	100	101	195..2561
OV43	MSLN: mesothelin, variant 6	153	154	88..1956

Definitions

5 As used herein, each of the following terms has the meaning associated with it in this section.

The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.* to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

10 A "marker" is a gene whose altered level of expression in a tissue or cell from its expression level in normal or healthy tissue or cell is associated with a disease state, such as cancer. A "marker nucleic acid" is a nucleic acid (*e.g.*, mRNA, cDNA) encoded by or corresponding to a marker of the invention. Such marker nucleic acids include DNA (*e.g.*, cDNA) comprising the entire or a partial sequence of any of the
15 nucleic acid sequences set forth in the Sequence Listing or the complement of such a sequence. The marker nucleic acids also include RNA comprising the entire or a partial sequence of any of the nucleic acid sequences set forth in the Sequence Listing or the complement of such a sequence, wherein all thymidine residues are replaced with uridine residues. A "marker protein" is a protein encoded by or corresponding to a
20 marker of the invention. A marker protein comprises the entire or a partial sequence of any of the sequences set forth in the Sequence Listing. The terms "protein" and "polypeptide" are used interchangeably.

The term "probe" refers to any molecule which is capable of selectively binding to a specifically intended target molecule, for example, a nucleotide transcript or
25 protein encoded by or corresponding to a marker. Probes can be either synthesized by one skilled in the art, or derived from appropriate biological preparations. For purposes of detection of the target molecule, probes may be specifically designed to be labeled, as

described herein. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

A "cervical-associated" body fluid is a fluid which, when in the body of a patient, contacts or passes through cervical cells or into which cells or proteins shed from cervical cells are capable of passing. The cells may be found in a cervical smear collected, for example, by a cervical brush. Exemplary cervical-associated body fluids include blood fluids, lymph, ascitic fluids, gynecological fluids, cystic fluid, urine, and fluids collected by vaginal rinsing.

The "normal" level of expression of a marker is the level of expression of the marker in cervical cells of a human subject or patient not afflicted with cervical cancer

An "over-expression" or "significantly higher level of expression" of a marker refers to an expression level in a test sample that is greater than the standard error of the assay employed to assess expression, and is preferably at least twice, and more preferably three, four, five or ten times the expression level of the marker in a control sample (*e.g.*, sample from a healthy subjects not having the marker associated disease) and preferably, the average expression level of the marker in several control samples.

A "significantly lower level of expression" of a marker refers to an expression level in a test sample that is at least twice, and more preferably three, four, five or ten times lower than the expression level of the marker in a control sample (*e.g.*, sample from a healthy subject not having the marker associated disease) and preferably, the average expression level of the marker in several control samples.

As used herein, the term "promoter/regulatory sequence" means a nucleic acid sequence which is required for expression of a gene product operably linked to the promoter/regulatory sequence. In some instances, this sequence may be the core promoter sequence and in other instances, this sequence may also include an enhancer sequence and other regulatory elements which are required for expression of the gene product. The promoter/regulatory sequence may, for example, be one which expresses the gene product in a tissue-specific manner.

A "constitutive" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell under most or all physiological conditions of the cell.

- 5 An "inducible" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only when an inducer which corresponds to the promoter is present in the cell.

- 10 A "tissue-specific" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only if the cell is a cell of the tissue type corresponding to the promoter.

- 15 A "transcribed polynucleotide" or "nucleotide transcript" is a polynucleotide (*e.g.* an mRNA, hnRNA, a cDNA, or an analog of such RNA or cDNA) which is complementary to or homologous with all or a portion of a mature mRNA made by transcription of a marker of the invention and normal post-transcriptional processing (*e.g.* splicing), if any, of the RNA transcript, and reverse transcription of the RNA transcript.

- 20 "Complementary" refers to the broad concept of sequence complementarity between regions of two nucleic acid strands or between two regions of the same nucleic acid strand. It is known that an adenine residue of a first nucleic acid region is capable of forming specific hydrogen bonds ("base pairing") with a residue of a second nucleic acid region which is antiparallel to the first region if the residue is thymine or uracil. Similarly, it is known that a cytosine residue of a first nucleic acid strand is capable of base pairing with a residue of a second nucleic acid strand which is antiparallel to the first strand if the residue is guanine. A first region of a nucleic acid is complementary to a second region of the same or a different nucleic acid if, when the two regions are arranged in an antiparallel fashion, at least one nucleotide residue of the first region is capable of base pairing with a residue of the second region. Preferably, 25 the first region comprises a first portion and the second region comprises a second portion, whereby, when the first and second portions are arranged in an antiparallel fashion, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residues of the first portion are capable of base pairing 30

with nucleotide residues in the second portion. More preferably, all nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion.

"Homologous" as used herein, refers to nucleotide sequence similarity
5 between two regions of the same nucleic acid strand or between regions of two different nucleic acid strands. When a nucleotide residue position in both regions is occupied by the same nucleotide residue, then the regions are homologous at that position. A first region is homologous to a second region if at least one nucleotide residue position of each region is occupied by the same residue. Homology between two regions is
10 expressed in terms of the proportion of nucleotide residue positions of the two regions that are occupied by the same nucleotide residue. By way of example, a region having the nucleotide sequence 5'-ATTGCC-3' and a region having the nucleotide sequence 5'-TATGGC-3' share 50% homology. Preferably, the first region comprises a first portion and the second region comprises a second portion, whereby, at least about 50%, and
15 preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residue positions of each of the portions are occupied by the same nucleotide residue. More preferably, all nucleotide residue positions of each of the portions are occupied by the same nucleotide residue.

A molecule is "fixed" or "affixed" to a substrate if it is covalently or non-
20 covalently associated with the substrate such the substrate can be rinsed with a fluid (*e.g.* standard saline citrate, pH 7.4) without a substantial fraction of the molecule dissociating from the substrate.

As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in an organism found
25 in nature.

A cancer is "inhibited" if at least one symptom of the cancer is alleviated, terminated, slowed, or prevented. As used herein, cervical cancer is also "inhibited" if recurrence or metastasis of the cancer is reduced, slowed, delayed, or prevented.

A kit is any manufacture (*e.g.* a package or container) comprising at least
30 one reagent, *e.g.* a probe, for specifically detecting the expression of a marker of the invention. The kit may be promoted, distributed, or sold as a unit for performing the methods of the present invention.

“Proteins of the invention” encompass marker proteins and their fragments; variant marker proteins and their fragments; peptides and polypeptides comprising an at least 15 amino acid segment of a marker or variant marker protein; and fusion proteins comprising a marker or variant marker protein, or an at least 15 amino acid segment of a marker or variant marker protein.

Unless otherwise specified herewithin, the terms “antibody” and “antibodies” broadly encompass naturally-occurring forms of antibodies (*e.g.*, IgG, IgA, IgM, IgE) and recombinant antibodies such as single-chain antibodies, chimeric and humanized antibodies and multi-specific antibodies, as well as fragments and derivatives of all of the foregoing, which fragments and derivatives have at least an antigenic binding site. Antibody derivatives may comprise a protein or chemical moiety conjugated to an antibody.

Description

The present invention is based, in part, on newly identified markers which are over-expressed in cervical cancer cells as compared to their expression in normal (*i.e.* non-cancerous) cervical cells. The enhanced expression of one or more of these markers in cervical cells is herein correlated with the cancerous state of the tissue. The invention provides compositions, kits, and methods for assessing the cancerous state of cervical cells (*e.g.* cells obtained from a human, cultured human cells, archived or preserved human cells and *in vivo* cells) as well as treating patients afflicted with cervical cancer.

The compositions, kits, and methods of the invention have the following uses, among others:

- 1) assessing whether a patient is afflicted with cervical cancer;
- 2) assessing the stage of cervical cancer in a human patient;
- 3) assessing the grade of cervical cancer in a patient;
- 4) assessing the benign or malignant nature of cervical cancer in a patient;
- 5) assessing the metastatic potential of cervical cancer in a patient;
- 6) assessing the histological type of neoplasm associated with cervical cancer in a patient;

- 7) making antibodies, antibody fragments or antibody derivatives that are useful for treating cervical cancer and/or assessing whether a patient is afflicted with cervical cancer;
- 8) assessing the presence of cervical cancer cells;
- 5 9) assessing the efficacy of one or more test compounds for inhibiting cervical cancer in a patient;
- 10 10) assessing the efficacy of a therapy for inhibiting cervical cancer in a patient;
- 11) monitoring the progression of cervical cancer in a patient;
- 10 12) selecting a composition or therapy for inhibiting cervical cancer in a patient;
- 13) treating a patient afflicted with cervical cancer;
- 14) inhibiting cervical cancer in a patient;
- 15 15) assessing the cervical carcinogenic potential of a test compound; and
- 16) preventing the onset of cervical cancer in a patient at risk for developing cervical cancer.

The invention thus includes a method of assessing whether a patient is afflicted with cervical cancer which includes assessing whether the patient has pre-
20 metastasized cervical cancer. This method comprises comparing the level of expression of a marker of the invention (listed in Table 1) in a patient sample and the normal level of expression of the marker in a control, *e.g.*, a non-cervical cancer sample. A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with cervical cancer.

25 Gene delivery vehicles, host cells and compositions (all described herein) containing nucleic acids comprising the entirety, or a segment of 15 or more nucleotides, of any of the nucleic acid sequences set forth in the Sequence Listing, or the complement of such sequences, and polypeptides comprising the entirety, or a segment of 10 or more amino acids, of any of the amino acid sequences set forth in the Sequence
30 Listing, are also provided by this invention.

As described herein, cervical cancer in patients is associated with an increased level of expression of one or more markers of the invention. While, as discussed above, some of these changes in expression level result from occurrence of the

cervical cancer, others of these changes induce, maintain, and promote the cancerous state of cervical cancer cells. Thus, cervical cancer characterized by an increase in the level of expression of one or more markers of the invention can be inhibited by reducing and/or interfering with the expression of the markers and/or function of the proteins encoded by those markers.

Expression of a marker of the invention can be inhibited in a number of ways generally known in the art. For example, an antisense oligonucleotide can be provided to the cervical cancer cells in order to inhibit transcription, translation, or both, of the marker(s). Alternately, a polynucleotide encoding an antibody, an antibody derivative, or an antibody fragment which specifically binds a marker protein, and operably linked with an appropriate promoter/regulator region, can be provided to the cell in order to generate intracellular antibodies which will inhibit the function or activity of the protein. The expression and/or function of a marker may also be inhibited by treating the cervical cancer cell with an antibody, antibody derivative or antibody fragment that specifically binds a marker protein. Using the methods described herein, a variety of molecules, particularly including molecules sufficiently small that they are able to cross the cell membrane, can be screened in order to identify molecules which inhibit expression of a marker or inhibit the function of a marker protein. The compound so identified can be provided to the patient in order to inhibit cervical cancer cells of the patient.

Any marker or combination of markers of the invention, as well as any known markers in combination with the markers of the invention, may be used in the compositions, kits, and methods of the present invention. In general, it is preferable to use markers for which the difference between the level of expression of the marker in cervical cancer cells and the level of expression of the same marker in normal cervical cells is as great as possible. Although this difference can be as small as the limit of detection of the method for assessing expression of the marker, it is preferred that the difference be at least greater than the standard error of the assessment method, and preferably a difference of at least 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 15-, 20-, 25-, 100-, 500-, 1000-fold or greater than the level of expression of the same marker in normal cervical tissue.

It is recognized that certain marker proteins are secreted from cervical cells (*i.e.* one or both of normal and cancerous cells) to the extracellular space surrounding the cells. These markers are preferably used in certain embodiments of the compositions, kits, and methods of the invention, owing to the fact that the such marker proteins can be detected in a cervical-associated body fluid sample, which may be more easily collected from a human patient than a tissue biopsy sample. In addition, preferred *in vivo* techniques for detection of a marker protein include introducing into a subject a labeled antibody directed against the protein. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

It is a simple matter for the skilled artisan to determine whether any particular marker protein is a secreted protein. In order to make this determination, the marker protein is expressed in, for example, a mammalian cell, preferably a human cervical cell line, extracellular fluid is collected, and the presence or absence of the protein in the extracellular fluid is assessed (*e.g.* using a labeled antibody which binds specifically with the protein).

The following is an example of a method which can be used to detect secretion of a protein. About 8×10^5 293T cells are incubated at 37°C in wells containing growth medium (Dulbecco's modified Eagle's medium {DMEM} supplemented with 10% fetal bovine serum) under a 5% (v/v) CO₂, 95% air atmosphere to about 60-70% confluence. The cells are then transfected using a standard transfection mixture comprising 2 micrograms of DNA comprising an expression vector encoding the protein and 10 microliters of LipofectAMINE™ (GIBCO/BRL Catalog no. 18342-012) per well. The transfection mixture is maintained for about 5 hours, and then replaced with fresh growth medium and maintained in an air atmosphere. Each well is gently rinsed twice with DMEM which does not contain methionine or cysteine (DMEM-MC; ICN Catalog no. 16-424-54). About 1 milliliter of DMEM-MC and about 50 microcuries of Trans-³⁵S™ reagent (ICN Catalog no. 51006) are added to each well. The wells are maintained under the 5% CO₂ atmosphere described above and incubated at 37°C for a selected period. Following incubation, 150 microliters of conditioned medium is removed and centrifuged to remove floating cells and debris.

The presence of the protein in the supernatant is an indication that the protein is secreted.

It will be appreciated that patient samples containing cervical cells may be used in the methods of the present invention. In these embodiments, the level of expression of the marker can be assessed by assessing the amount (*e.g.* absolute amount or concentration) of the marker in a cervical cell sample, *e.g.*, cervical smear obtained from a patient. The cell sample can, of course, be subjected to a variety of well-known post-collection preparative and storage techniques (*e.g.*, nucleic acid and/or protein extraction, fixation, storage, freezing, ultrafiltration, concentration, evaporation, centrifugation, etc.) prior to assessing the amount of the marker in the sample. Likewise, cervical smears may also be subjected to post-collection preparative and storage techniques, *e.g.*, fixation.

The compositions, kits, and methods of the invention can be used to detect expression of marker proteins having at least one portion which is displayed on the surface of cells which express it. It is a simple matter for the skilled artisan to determine whether a marker protein, or a portion thereof, is exposed on the cell surface. For example, immunological methods may be used to detect such proteins on whole cells, or well known computer-based sequence analysis methods may be used to predict the presence of at least one extracellular domain (*i.e.* including both secreted proteins and proteins having at least one cell-surface domain). Expression of a marker protein having at least one portion which is displayed on the surface of a cell which expresses it may be detected without necessarily lysing the cell (*e.g.* using a labeled antibody which binds specifically with a cell-surface domain of the protein).

Expression of a marker of the invention may be assessed by any of a wide variety of well known methods for detecting expression of a transcribed nucleic acid or protein. Non-limiting examples of such methods include immunological methods for detection of secreted, cell-surface, cytoplasmic, or nuclear proteins, protein purification methods, protein function or activity assays, nucleic acid hybridization methods, nucleic acid reverse transcription methods, and nucleic acid amplification methods.

In a preferred embodiment, expression of a marker is assessed using an antibody (*e.g.* a radio-labeled, chromophore-labeled, fluorophore-labeled, or enzyme-labeled antibody), an antibody derivative (*e.g.* an antibody conjugated with a substrate or with the protein or ligand of a protein-ligand pair {*e.g.* biotin-streptavidin}), or an

antibody fragment (*e.g.* a single-chain antibody, an isolated antibody hypervariable domain, etc.) which binds specifically with a marker protein or fragment thereof, including a marker protein which has undergone all or a portion of its normal post-translational modification.

5 In another preferred embodiment, expression of a marker is assessed by preparing mRNA/cDNA (*i.e.* a transcribed polynucleotide) from cells in a patient sample, and by hybridizing the mRNA/cDNA with a reference polynucleotide which is a complement of a marker nucleic acid, or a fragment thereof. cDNA can, optionally, be amplified using any of a variety of polymerase chain reaction methods prior to
10 hybridization with the reference polynucleotide; preferably, it is not amplified. Expression of one or more markers can likewise be detected using quantitative PCR to assess the level of expression of the marker(s). Alternatively, any of the many known methods of detecting mutations or variants (*e.g.* single nucleotide polymorphisms, deletions, etc.) of a marker of the invention may be used to detect occurrence of a
15 marker in a patient.

 In a related embodiment, a mixture of transcribed polynucleotides obtained from the sample is contacted with a substrate having fixed thereto a polynucleotide complementary to or homologous with at least a portion (*e.g.* at least 7,
10, 15, 20, 25, 30, 40, 50, 100, 500, or more nucleotide residues) of a marker nucleic
20 acid. If polynucleotides complementary to or homologous with are differentially detectable on the substrate (*e.g.* detectable using different chromophores or fluorophores, or fixed to different selected positions), then the levels of expression of a plurality of markers can be assessed simultaneously using a single substrate (*e.g.* a "gene chip" microarray of polynucleotides fixed at selected positions). When a method of
25 assessing marker expression is used which involves hybridization of one nucleic acid with another, it is preferred that the hybridization be performed under stringent hybridization conditions.

 Because the compositions, kits, and methods of the invention rely on detection of a difference in expression levels of one or more markers of the invention, it
30 is preferable that the level of expression of the marker is significantly greater than the minimum detection limit of the method used to assess expression in at least one of normal cervical cells and cancerous cervical cells.

It is understood that by routine screening of additional patient samples using one or more of the markers of the invention, it will be realized that certain of the markers are over-expressed in cancers of various types, including specific cervical cancers, as well as other cancers such as breast cancer, ovarian cancer, etc. For example, it will be confirmed that some of the markers of the invention are over-expressed in most (*i.e.* 50% or more) or substantially all (*i.e.* 80% or more) of cervical cancer. Furthermore, it will be confirmed that certain of the markers of the invention are associated with cervical cancer of various stages (*i.e.* stage 0, I, II, III, and IV cervical cancers, as well as subclassifications IA1, IA2, IB, IB1, IB2, IIA, IIB, IIIA, IIIB, IVA, and IVB, using the FIGO Stage Grouping system for primary carcinoma of the cervix (see *Gynecologic Oncology*, 1991, 41:199 and *Cancer*, 1992, 69:482)), and pre-malignant conditions (*e.g.*, dysplasia including CIN or SIL), of various histologic subtypes (*e.g.* squamous cell carcinomas and squamous cell carcinoma variants such as verrucous carcinoma, lymphoepithelioma-like carcinoma, papillary squamous neoplasm and spindle cell squamous cell carcinoma (see *Cervical Cancer and Preinvasive Neoplasia*, 1996, pp. 90-91) serous, mucinous, endometrioid, and clear cell subtypes, as well as subclassifications and alternate classifications adenocarcinoma, papillary adenocarcinoma, papillary cystadenocarcinoma, surface papillary carcinoma, malignant adenofibroma, cystadenofibroma, adenocarcinoma, cystadenocarcinoma, adenoacanthoma, endometrioid stromal sarcoma, mesodermal {Müllerian} mixed tumor, malignant carcinoma, Brenner tumor, mixed epithelial tumor, and undifferentiated carcinoma, using the WHO/FIGO system for classification of malignant cervical tumors; Scully, *Atlas of Tumor Pathology*, 3d series, Washington DC), and various grades (*i.e.* grade I {well differentiated}, grade II {moderately well differentiated}, and grade III {poorly differentiated from surrounding normal tissue}). In addition, as a greater number of patient samples are assessed for expression of the markers of the invention and the outcomes of the individual patients from whom the samples were obtained are correlated, it will also be confirmed that altered expression of certain of the markers of the invention are strongly correlated with malignant cancers and that altered expression of other markers of the invention are strongly correlated with benign tumors. The compositions, kits, and methods of the invention are thus useful for characterizing one or more of the stage, grade, histological type, and benign/malignant nature of cervical cancer in patients.

When the compositions, kits, and methods of the invention are used for characterizing one or more of the stage, grade, histological type, and benign/malignant nature of cervical cancer in a patient, it is preferred that the marker or panel of markers of the invention is selected such that a positive result is obtained in at least about 20%,
5 and preferably at least about 40%, 60%, or 80%, and more preferably in substantially all patients afflicted with a cervical cancer of the corresponding stage, grade, histological type, or benign/malignant nature. Preferably, the marker or panel of markers of the invention is selected such that a positive predictive value (PPV) of greater than about 10% is obtained for the general population (more preferably coupled with an assay
10 specificity greater than 80%).

When a plurality of markers of the invention are used in the compositions, kits, and methods of the invention, the level of expression of each marker in a patient sample can be compared with the normal level of expression of each of the plurality of markers in non-cancerous samples of the same type, either in a single
15 reaction mixture (*i.e.* using reagents, such as different fluorescent probes, for each marker) or in individual reaction mixtures corresponding to one or more of the markers. In one embodiment, a significantly increased level of expression of more than one of the plurality of markers in the sample, relative to the corresponding normal levels, is an indication that the patient is afflicted with cervical cancer. When a plurality of markers
20 is used, it is preferred that 2, 3, 4, 5, 8, 10, 12, 15, 20, 30, or 50 or more individual markers be used, wherein fewer markers are preferred.

In order to maximize the sensitivity of the compositions, kits, and methods of the invention (*i.e.* by interference attributable to cells of non-cervical origin in a patient sample), it is preferable that the marker of the invention used therein be a
25 marker which has a restricted tissue distribution, *e.g.*, normally not expressed in a non-cervical tissue.

Only a small number of markers are known to be associated with cervical cancer (*e.g.* bcl-2, 15A8 antigen, cdc6, Mcm5, and EGFR). These markers are not, of course, included among the markers of the invention, although they may be used
30 together with one or more markers of the invention in a panel of markers, for example. It is well known that certain types of genes, such as oncogenes, tumor suppressor genes, growth factor-like genes, protease-like genes, and protein kinase-like genes are often involved with development of cancers of various types. Thus, among the markers of the

invention, use of those which correspond to proteins which resemble known proteins encoded by known oncogenes and tumor suppressor genes, and those which correspond to proteins which resemble growth factors, proteases, and protein kinases are preferred.

It is recognized that the compositions, kits, and methods of the invention will be of particular utility to patients having an enhanced risk of developing cervical cancer and their medical advisors. Patients recognized as having an enhanced risk of developing cervical cancer include, for example, patients having a familial history of cervical cancer, patients identified as having a mutant oncogene (*i.e.* at least one allele), and patients of advancing age (*i.e.* women older than about 50 or 60 years).

The level of expression of a marker in normal (*i.e.* non-cancerous) human cervical tissue can be assessed in a variety of ways. In one embodiment, this normal level of expression is assessed by assessing the level of expression of the marker in a portion of cervical cells which appears to be non-cancerous and by comparing this normal level of expression with the level of expression in a portion of the cervical cells which is suspected of being cancerous. Alternately, and particularly as further information becomes available as a result of routine performance of the methods described herein, population-average values for normal expression of the markers of the invention may be used. In other embodiments, the 'normal' level of expression of a marker may be determined by assessing expression of the marker in a patient sample obtained from a non-cancer-afflicted patient, from a patient sample obtained from a patient before the suspected onset of cervical cancer in the patient, from archived patient samples, and the like.

The invention includes compositions, kits, and methods for assessing the presence of cervical cancer cells in a sample (*e.g.* an archived tissue sample or a sample obtained from a patient). These compositions, kits, and methods are substantially the same as those described above, except that, where necessary, the compositions, kits, and methods are adapted for use with samples other than patient samples. For example, when the sample to be used is a parafinized, archived human tissue sample, it can be necessary to adjust the ratio of compounds in the compositions of the invention, in the kits of the invention, or the methods used to assess levels of marker expression in the sample. Such methods are well known in the art and within the skill of the ordinary artisan.

The invention includes a kit for assessing the presence of cervical cancer cells (*e.g.* in a sample such as a patient sample). The kit comprises a plurality of reagents, each of which is capable of binding specifically with a marker nucleic acid or protein. Suitable reagents for binding with a marker protein include antibodies, antibody
5 derivatives, antibody fragments, and the like. Suitable reagents for binding with a marker nucleic acid (*e.g.* a genomic DNA, an mRNA, a spliced mRNA, a cDNA, or the like) include complementary nucleic acids. For example, the nucleic acid reagents may include oligonucleotides (labeled or non-labeled) fixed to a substrate, labeled
oligonucleotides not bound with a substrate, pairs of PCR primers, molecular beacon
10 probes, and the like.

The kit of the invention may optionally comprise additional components useful for performing the methods of the invention. By way of example, the kit may comprise fluids (*e.g.* SSC buffer) suitable for annealing complementary nucleic acids or
for binding an antibody with a protein with which it specifically binds, one or more
15 sample compartments, an instructional material which describes performance of a method of the invention, a sample of normal cervical cells, a sample of cervical cancer cells, and the like.

The invention also includes a method of making an isolated hybridoma which produces an antibody useful for assessing whether patient is afflicted with an
20 cervical cancer. In this method, a protein or peptide comprising the entirety or a segment of a marker protein is synthesized or isolated (*e.g.* by purification from a cell in which it is expressed or by transcription and translation of a nucleic acid encoding the protein or peptide *in vivo* or *in vitro* using known methods). A vertebrate, preferably a mammal such as a mouse, rat, rabbit, or sheep, is immunized using the protein or
25 peptide. The vertebrate may optionally (and preferably) be immunized at least one additional time with the protein or peptide, so that the vertebrate exhibits a robust immune response to the protein or peptide. Splenocytes are isolated from the immunized vertebrate and fused with an immortalized cell line to form hybridomas, using any of a variety of methods well known in the art. Hybridomas formed in this
30 manner are then screened using standard methods to identify one or more hybridomas which produce an antibody which specifically binds with the marker protein or a fragment thereof. The invention also includes hybridomas made by this method and antibodies made using such hybridomas.

The invention also includes a method of assessing the efficacy of a test compound for inhibiting cervical cancer cells. As described above, differences in the level of expression of the markers of the invention correlate with the cancerous state of cervical cells. Although it is recognized that changes in the levels of expression of certain of the markers of the invention likely result from the cancerous state of cervical cells, it is likewise recognized that changes in the levels of expression of other of the markers of the invention induce, maintain, and promote the cancerous state of those cells. Thus, compounds which inhibit an cervical cancer in a patient will cause the level of expression of one or more of the markers of the invention to change to a level nearer the normal level of expression for that marker (*i.e.* the level of expression for the marker in non-cancerous cervical cells).

This method thus comprises comparing expression of a marker in a first cervical cell sample and maintained in the presence of the test compound and expression of the marker in a second cervical cell sample and maintained in the absence of the test compound. A significantly reduced expression of a marker of the invention in the presence of the test compound is an indication that the test compound inhibits cervical cancer. The cervical cell samples may, for example, be aliquots of a single sample of normal cervical cells obtained from a patient, pooled samples of normal cervical cells obtained from a patient, cells of a normal cervical cell line, aliquots of a single sample of cervical cancer cells obtained from a patient, pooled samples of cervical cancer cells obtained from a patient, cells of an cervical cancer cell line, or the like. In one embodiment, the samples are cervical cancer cells obtained from a patient and a plurality of compounds known to be effective for inhibiting various cervical cancers are tested in order to identify the compound which is likely to best inhibit the cervical cancer in the patient.

This method may likewise be used to assess the efficacy of a therapy for inhibiting cervical cancer in a patient. In this method, the level of expression of one or more markers of the invention in a pair of samples (one subjected to the therapy, the other not subjected to the therapy) is assessed. As with the method of assessing the efficacy of test compounds, if the therapy induces a significantly lower level of expression of a marker of the invention then the therapy is efficacious for inhibiting cervical cancer. As above, if samples from a selected patient are used in this method,

then alternative therapies can be assessed *in vitro* in order to select a therapy most likely to be efficacious for inhibiting cervical cancer in the patient.

As described above, the cancerous state of human cervical cells is correlated with changes in the levels of expression of the markers of the invention. The invention includes a method for assessing the human cervical cell carcinogenic potential of a test compound. This method comprises maintaining separate aliquots of human cervical cells in the presence and absence of the test compound. Expression of a marker of the invention in each of the aliquots is compared. A significantly higher level of expression of a marker of the invention in the aliquot maintained in the presence of the test compound (relative to the aliquot maintained in the absence of the test compound) is an indication that the test compound possesses human cervical cell carcinogenic potential. The relative carcinogenic potentials of various test compounds can be assessed by comparing the degree of enhancement or inhibition of the level of expression of the relevant markers, by comparing the number of markers for which the level of expression is enhanced or inhibited, or by comparing both.

Various aspects of the invention are described in further detail in the following subsections.

I. Isolated Nucleic Acid Molecules

One aspect of the invention pertains to isolated nucleic acid molecules, including nucleic acids which encode a marker protein or a portion thereof. Isolated nucleic acids of the invention also include nucleic acid molecules sufficient for use as hybridization probes to identify marker nucleic acid molecules, and fragments of marker nucleic acid molecules, *e.g.*, those suitable for use as PCR primers for the amplification or mutation of marker nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA) and RNA molecules (*e.g.*, mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. Preferably, an "isolated" nucleic acid molecule is free of sequences (preferably protein-encoding sequences) which naturally flank the nucleic acid (*i.e.*,

sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated nucleic acid molecule can contain less than about 5 kB, 4 kB, 3 kB, 2 kB, 1 kB, 0.5 kB or 0.1 kB of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized.

10 A nucleic acid molecule of the present invention can be isolated using standard molecular biology techniques and the sequence information in the database records described herein. Using all or a portion of such nucleic acid sequences, nucleic acid molecules of the invention can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook *et al.*, ed., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 15 1989).

 A nucleic acid molecule of the invention can be amplified using cDNA, mRNA, or genomic DNA as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, nucleotides corresponding to all or a portion of a nucleic acid molecule of the invention can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

 In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which has a nucleotide sequence complementary to the nucleotide sequence of a marker nucleic acid or to the nucleotide sequence of a nucleic acid encoding a marker protein. A nucleic acid molecule which is complementary to a given nucleotide sequence is one which is sufficiently complementary to the given nucleotide sequence that it can hybridize to the given nucleotide sequence thereby forming a stable duplex.

 Moreover, a nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence, wherein the full length nucleic acid sequence comprises a marker nucleic acid or which encodes a marker protein. Such nucleic acids

can be used, for example, as a probe or primer. The probe/primer typically is used as one or more substantially purified oligonucleotides. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 7, preferably about 15, more preferably about 25, 50, 75, 100, 125, 150,
5 175, 200, 250, 300, 350, or 400 or more consecutive nucleotides of a nucleic acid of the invention.

Probes based on the sequence of a nucleic acid molecule of the invention can be used to detect transcripts or genomic sequences corresponding to one or more markers of the invention. The probe comprises a label group attached thereto, *e.g.*, a
10 radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as part of a diagnostic test kit for identifying cells or tissues which mis-express the protein, such as by measuring levels of a nucleic acid molecule encoding the protein in a sample of cells from a subject, *e.g.*, detecting mRNA levels or determining whether a gene encoding the protein has been mutated or deleted.

15 The invention further encompasses nucleic acid molecules that differ, due to degeneracy of the genetic code, from the nucleotide sequence of nucleic acids encoding a marker protein (*e.g.*, a protein having one of the amino acid sequences set forth in the Sequence Listing), and thus encode the same protein.

It will be appreciated by those skilled in the art that DNA sequence
20 polymorphisms that lead to changes in the amino acid sequence can exist within a population (*e.g.*, the human population). Such genetic polymorphisms can exist among individuals within a population due to natural allelic variation. An allele is one of a group of genes which occur alternatively at a given genetic locus. In addition, it will be appreciated that DNA polymorphisms that affect RNA expression levels can also exist
25 that may affect the overall expression level of that gene (*e.g.*, by affecting regulation or degradation).

As used herein, the phrase "allelic variant" refers to a nucleotide sequence which occurs at a given locus or to a polypeptide encoded by the nucleotide sequence.

As used herein, the terms "gene" and "recombinant gene" refer to nucleic
30 acid molecules comprising an open reading frame encoding a polypeptide corresponding to a marker of the invention. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of a given gene. Alternative alleles can be identified by sequencing the gene of interest in a number of different individuals. This can be

readily carried out by using hybridization probes to identify the same genetic locus in a variety of individuals. Any and all such nucleotide variations and resulting amino acid polymorphisms or variations that are the result of natural allelic variation and that do not alter the functional activity are intended to be within the scope of the invention.

5 In another embodiment, an isolated nucleic acid molecule of the invention is at least 7, 15, 20, 25, 30, 40, 60, 80, 100, 150, 200, 250, 300, 350, 400, 450, 550, 650, 700, 800, 900, 1000, 1200, 1400, 1600, 1800, 2000, 2200, 2400, 2600, 2800, 3000, 3500, 4000, 4500, or more nucleotides in length and hybridizes under stringent conditions to a marker nucleic acid or to a nucleic acid encoding a marker protein. As
10 used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% (65%, 70%, preferably 75%) identical to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in sections 6.3.1-6.3.6 of *Current Protocols in Molecular Biology*, John Wiley & Sons,
15 N.Y. (1989). A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50-65°C.

 In addition to naturally-occurring allelic variants of a nucleic acid molecule of the invention that can exist in the population, the skilled artisan will further
20 appreciate that sequence changes can be introduced by mutation thereby leading to changes in the amino acid sequence of the encoded protein, without altering the biological activity of the protein encoded thereby. For example, one can make nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues. A "non-essential" amino acid residue is a residue that can be altered from
25 the wild-type sequence without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are not conserved or only semi-conserved among homologs of various species may be non-essential for activity and thus would be likely targets for alteration.
 Alternatively, amino acid residues that are conserved among the homologs of various
30 species (*e.g.*, murine and human) may be essential for activity and thus would not be likely targets for alteration.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding a variant marker protein that contain changes in amino acid residues that are not essential for activity. Such variant marker proteins differ in amino acid sequence from the naturally-occurring marker proteins, yet retain biological activity. In one embodiment, such a variant marker protein has an amino acid sequence that is at least about 40% identical, 50%, 60%, 70%, 80%, 90%, 95%, or 98% identical to the amino acid sequence of a marker protein.

An isolated nucleic acid molecule encoding a variant marker protein can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of marker nucleic acids, such that one or more amino acid residue substitutions, additions, or deletions are introduced into the encoded protein. Mutations can be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), non-polar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

The present invention encompasses antisense nucleic acid molecules, *i.e.*, molecules which are complementary to a sense nucleic acid of the invention, *e.g.*, complementary to the coding strand of a double-stranded marker cDNA molecule or complementary to a marker mRNA sequence. Accordingly, an antisense nucleic acid of the invention can hydrogen bond to (*i.e.* anneal with) a sense nucleic acid of the invention. The antisense nucleic acid can be complementary to an entire coding strand,

or to only a portion thereof, *e.g.*, all or part of the protein coding region (or open reading frame). An antisense nucleic acid molecule can also be antisense to all or part of a non-coding region of the coding strand of a nucleotide sequence encoding a marker protein. The non-coding regions ("5' and 3' untranslated regions") are the 5' and 3' sequences
5 which flank the coding region and are not translated into amino acids.

An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 or more nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an
10 antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which
15 can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-
20 methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-
25 methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been sub-cloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense
30 orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a marker protein to thereby inhibit expression of the marker, *e.g.*, by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. Examples of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site or infusion of the antisense nucleic acid into an ovary-associated body fluid. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, *e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

An antisense nucleic acid molecule of the invention can be an α -anomeric nucleic acid molecule. An α -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual α -units, the strands run parallel to each other (Gaultier *et al.*, 1987, *Nucleic Acids Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-O-methylribonucleotide (Inoue *et al.*, 1987, *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue *et al.*, 1987, *FEBS Lett.* 215:327-330).

The invention also encompasses ribozymes. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes as described in Haselhoff and Gerlach, 1988, *Nature* 334:585-591) can be used to catalytically cleave mRNA transcripts to thereby inhibit translation of the protein encoded by the mRNA. A ribozyme having specificity for a nucleic acid molecule encoding a marker protein can be designed based

upon the nucleotide sequence of a cDNA corresponding to the marker. For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved (see Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742).

5 Alternatively, an mRNA encoding a polypeptide of the invention can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules (see, *e.g.*, Bartel and Szostak, 1993, *Science* 261:1411-1418).

The invention also encompasses nucleic acid molecules which form triple helical structures. For example, expression of a marker of the invention can be inhibited
10 by targeting nucleotide sequences complementary to the regulatory region of the gene encoding the marker nucleic acid or protein (*e.g.*, the promoter and/or enhancer) to form triple helical structures that prevent transcription of the gene in target cells. See generally Helene (1991) *Anticancer Drug Des.* 6(6):569-84; Helene (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher (1992) *Bioassays* 14(12):807-15.

15 In various embodiments, the nucleic acid molecules of the invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids (see Hyrup *et al.*, 1996, *Bioorganic & Medicinal Chemistry* 4(1): 5-23). As used
20 herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, *e.g.*, DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be
25 performed using standard solid phase peptide synthesis protocols as described in Hyrup *et al.* (1996), *supra*; Perry-O'Keefe *et al.* (1996) *Proc. Natl. Acad. Sci. USA* 93:14670-675.

PNAs can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific
30 modulation of gene expression by, *e.g.*, inducing transcription or translation arrest or inhibiting replication. PNAs can also be used, *e.g.*, in the analysis of single base pair mutations in a gene by, *e.g.*, PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, *e.g.*, S1 nucleases (Hyrup

(1996), *supra*; or as probes or primers for DNA sequence and hybridization (Hyrup, 1996, *supra*; Perry-O'Keefe *et al.*, 1996, *Proc. Natl. Acad. Sci. USA* 93:14670-675).

In another embodiment, PNAs can be modified, *e.g.*, to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras can be generated which can combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, *e.g.*, RNase H and DNA polymerases, to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup, 1996, *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup (1996), *supra*, and Finn *et al.* (1996) *Nucleic Acids Res.* 24(17):3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs. Compounds such as 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite can be used as a link between the PNA and the 5' end of DNA (Mag *et al.*, 1989, *Nucleic Acids Res.* 17:5973-88). PNA monomers are then coupled in a step-wise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn *et al.*, 1996, *Nucleic Acids Res.* 24(17):3357-63). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser *et al.*, 1975, *Bioorganic Med. Chem. Lett.* 5:1119-1124).

In other embodiments, the oligonucleotide can include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.*, 1989, *Proc. Natl. Acad. Sci. USA* 86:6553-6556; Lemaitre *et al.*, 1987, *Proc. Natl. Acad. Sci. USA* 84:648-652; PCT Publication No. WO 88/09810) or the blood-brain barrier (see, *e.g.*, PCT Publication No. WO 89/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, 1988, *Bio/Techniques* 6:958-976) or intercalating agents (see, *e.g.*, Zon, 1988, *Pharm. Res.* 5:539-549). To this end, the oligonucleotide can be conjugated to another molecule, *e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The invention also includes molecular beacon nucleic acids having at least one region which is complementary to a nucleic acid of the invention, such that the molecular beacon is useful for quantitating the presence of the nucleic acid of the invention in a sample. A "molecular beacon" nucleic acid is a nucleic acid comprising a pair of complementary regions and having a fluorophore and a fluorescent quencher associated therewith. The fluorophore and quencher are associated with different portions of the nucleic acid in such an orientation that when the complementary regions are annealed with one another, fluorescence of the fluorophore is quenched by the quencher. When the complementary regions of the nucleic acid are not annealed with one another, fluorescence of the fluorophore is quenched to a lesser degree. Molecular beacon nucleic acids are described, for example, in U.S. Patent 5,876,930.

II. Isolated Proteins and Antibodies

One aspect of the invention pertains to isolated marker proteins and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise antibodies directed against a marker protein or a fragment thereof. In one embodiment, the native marker protein can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, a protein or peptide comprising the whole or a segment of the marker protein is produced by recombinant DNA techniques. Alternative to recombinant expression, such protein or peptide can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of protein in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, protein that is substantially free of cellular material includes preparations of protein having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). When the protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less

than about 20%, 10%, or 5% of the volume of the protein preparation. When the protein is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, *i.e.*, it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such
5 preparations of the protein have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the polypeptide of interest.

Biologically active portions of a marker protein include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the marker protein, which include fewer amino acids than the full
10 length protein, and exhibit at least one activity of the corresponding full-length protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the corresponding full-length protein. A biologically active portion of a marker protein of the invention can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acids in length. Moreover, other biologically active portions, in
15 which other regions of the marker protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of the native form of the marker protein.

Preferred marker proteins are encoded by nucleotide sequences comprising the sequence of any of the sequences set forth in the Sequence Listing.
20 Other useful proteins are substantially identical (*e.g.*, at least about 40%, preferably 50%, 60%, 70%, 80%, 90%, 95%, or 99%) to one of these sequences and retain the functional activity of the corresponding naturally-occurring marker protein yet differ in amino acid sequence due to natural allelic variation or mutagenesis.

To determine the percent identity of two amino acid sequences or of two
25 nucleic acids, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid
30 residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, %

identity = # of identical positions/total # of positions (e.g., overlapping positions) x100).

In one embodiment the two sequences are the same length.

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of 5 Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. Such an algorithm is incorporated into the BLASTN and BLASTX programs of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-410. BLAST nucleotide searches can be performed with 10 the BLASTN program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the BLASTP program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, a newer version of the BLAST algorithm called 15 Gapped BLAST can be utilized as described in Altschul *et al.* (1997) *Nucleic Acids Res.* 25:3389-3402, which is able to perform gapped local alignments for the programs BLASTN, BLASTP and BLASTX. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between molecules. When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the 20 respective programs (e.g., BLASTX and BLASTN) can be used. See <http://www.ncbi.nlm.nih.gov>. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, (1988) *CABIOS* 4:11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software 25 package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Yet another useful algorithm for identifying regions of local sequence similarity and alignment is the FASTA algorithm as described in Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85:2444-2448. When using the FASTA algorithm for 30 comparing nucleotide or amino acid sequences, a PAM120 weight residue table can, for example, be used with a *k*-tuple value of 2.

The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, only exact matches are counted.

The invention also provides chimeric or fusion proteins comprising a
5 marker protein or a segment thereof. As used herein, a "chimeric protein" or "fusion protein" comprises all or part (preferably a biologically active part) of a marker protein operably linked to a heterologous polypeptide (*i.e.*, a polypeptide other than the marker protein). Within the fusion protein, the term "operably linked" is intended to indicate that the marker protein or segment thereof and the heterologous polypeptide are fused
10 in-frame to each other. The heterologous polypeptide can be fused to the amino-terminus or the carboxyl-terminus of the marker protein or segment.

One useful fusion protein is a GST fusion protein in which a marker protein or segment is fused to the carboxyl terminus of GST sequences. Such fusion proteins can facilitate the purification of a recombinant polypeptide of the invention.

15 In another embodiment, the fusion protein contains a heterologous signal sequence at its amino terminus. For example, the native signal sequence of a marker protein can be removed and replaced with a signal sequence from another protein. For example, the gp67 secretory sequence of the baculovirus envelope protein can be used as a heterologous signal sequence (Ausubel *et al.*, ed., *Current Protocols in Molecular*
20 *Biology*, John Wiley & Sons, NY, 1992). Other examples of eukaryotic heterologous signal sequences include the secretory sequences of melittin and human placental alkaline phosphatase (Stratagene; La Jolla, California). In yet another example, useful prokaryotic heterologous signal sequences include the phoA secretory signal (Sambrook *et al.*, *supra*) and the protein A secretory signal (Pharmacia Biotech; Piscataway, New
25 Jersey).

In yet another embodiment, the fusion protein is an immunoglobulin fusion protein in which all or part of a marker protein is fused to sequences derived from a member of the immunoglobulin protein family. The immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered
30 to a subject to inhibit an interaction between a ligand (soluble or membrane-bound) and a protein on the surface of a cell (receptor), to thereby suppress signal transduction *in vivo*. The immunoglobulin fusion protein can be used to affect the bioavailability of a cognate ligand of a marker protein. Inhibition of ligand/receptor interaction can be

useful therapeutically, both for treating proliferative and differentiative disorders and for modulating (*e.g.* promoting or inhibiting) cell survival. Moreover, the immunoglobulin fusion proteins of the invention can be used as immunogens to produce antibodies directed against a marker protein in a subject, to purify ligands and in screening assays
5 to identify molecules which inhibit the interaction of the marker protein with ligands.

Chimeric and fusion proteins of the invention can be produced by standard recombinant DNA techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor
10 primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and re-amplified to generate a chimeric gene sequence (see, *e.g.*, Ausubel *et al.*, *supra*). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide). A nucleic acid encoding a polypeptide of the invention can be cloned into such an
15 expression vector such that the fusion moiety is linked in-frame to the polypeptide of the invention.

A signal sequence can be used to facilitate secretion and isolation of marker proteins. Signal sequences are typically characterized by a core of hydrophobic amino acids which are generally cleaved from the mature protein during secretion in one
20 or more cleavage events. Such signal peptides contain processing sites that allow cleavage of the signal sequence from the mature proteins as they pass through the secretory pathway. Thus, the invention pertains to marker proteins, fusion proteins or segments thereof having a signal sequence, as well as to such proteins from which the signal sequence has been proteolytically cleaved (*i.e.*, the cleavage products). In one
25 embodiment, a nucleic acid sequence encoding a signal sequence can be operably linked in an expression vector to a protein of interest, such as a marker protein or a segment thereof. The signal sequence directs secretion of the protein, such as from a eukaryotic host into which the expression vector is transformed, and the signal sequence is subsequently or concurrently cleaved. The protein can then be readily purified from the
30 extracellular medium by art recognized methods. Alternatively, the signal sequence can be linked to the protein of interest using a sequence which facilitates purification, such as with a GST domain.

The present invention also pertains to variants of the marker proteins.

Such variants have an altered amino acid sequence which can function as either agonists (mimetics) or as antagonists. Variants can be generated by mutagenesis, *e.g.*, discrete point mutation or truncation. An agonist can retain substantially the same, or a subset, of the biological activities of the naturally occurring form of the protein. An antagonist of a protein can inhibit one or more of the activities of the naturally occurring form of the protein by, for example, competitively binding to a downstream or upstream member of a cellular signaling cascade which includes the protein of interest. Thus, specific biological effects can be elicited by treatment with a variant of limited function.

10 Treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein can have fewer side effects in a subject relative to treatment with the naturally occurring form of the protein.

Variants of a marker protein which function as either agonists (mimetics) or as antagonists can be identified by screening combinatorial libraries of mutants, *e.g.*, truncation mutants, of the protein of the invention for agonist or antagonist activity. In one embodiment, a variegated library of variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential protein sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display). There are a variety of methods which can be used to produce libraries of potential variants of the marker proteins from a degenerate oligonucleotide sequence. Methods for synthesizing degenerate oligonucleotides are known in the art (see, *e.g.*, Narang, 1983, *Tetrahedron* 39:3; Itakura *et al.*, 1984, *Annu. Rev. Biochem.* 53:323; Itakura *et al.*, 1984, *Science* 198:1056; Ike *et al.*, 1983 *Nucleic Acid Res.* 11:477).

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In addition, libraries of segments of a marker protein can be used to generate a variegated population of polypeptides for screening and subsequent selection of variant marker proteins or segments thereof. For example, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of the coding sequence of interest with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different

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nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes amino terminal and internal fragments of various sizes of the protein of interest.

5 Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors,
10 transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify
15 variants of a protein of the invention (Arkin and Yourvan, 1992, *Proc. Natl. Acad. Sci. USA* 89:7811-7815; Delgrave *et al.*, 1993, *Protein Engineering* 6(3):327- 331).

Another aspect of the invention pertains to antibodies directed against a protein of the invention. In preferred embodiments, the antibodies specifically bind a marker protein or a fragment thereof. The terms "antibody" and "antibodies" as used
20 interchangeably herein refer to immunoglobulin molecules as well as fragments and derivatives thereof that comprise an immunologically active portion of an immunoglobulin molecule, (*i.e.*, such a portion contains an antigen binding site which specifically binds an antigen, such as a marker protein, *e.g.*, an epitope of a marker protein). An antibody which specifically binds to a protein of the invention is an
25 antibody which binds the protein, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample, which naturally contains the protein. Examples of an immunologically active portion of an immunoglobulin molecule include, but are not limited to, single-chain antibodies (scAb), F(ab) and F(ab')₂ fragments.

An isolated protein of the invention or a fragment thereof can be used as
30 an immunogen to generate antibodies. The full-length protein can be used or, alternatively, the invention provides antigenic peptide fragments for use as immunogens. The antigenic peptide of a protein of the invention comprises at least 8 (preferably 10, 15, 20, or 30 or more) amino acid residues of the amino acid sequence of one of the

proteins of the invention, and encompasses at least one epitope of the protein such that an antibody raised against the peptide forms a specific immune complex with the protein. Preferred epitopes encompassed by the antigenic peptide are regions that are located on the surface of the protein, *e.g.*, hydrophilic regions. Hydrophobicity sequence analysis, hydrophilicity sequence analysis, or similar analyses can be used to identify hydrophilic regions. In preferred embodiments, an isolated marker protein or fragment thereof is used as an immunogen.

An immunogen typically is used to prepare antibodies by immunizing a suitable (*i.e.* immunocompetent) subject such as a rabbit, goat, mouse, or other mammal or vertebrate. An appropriate immunogenic preparation can contain, for example, recombinantly-expressed or chemically-synthesized protein or peptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or a similar immunostimulatory agent. Preferred immunogen compositions are those that contain no other human proteins such as, for example, immunogen compositions made using a non-human host cell for recombinant expression of a protein of the invention. In such a manner, the resulting antibody compositions have reduced or no binding of human proteins other than a protein of the invention.

The invention provides polyclonal and monoclonal antibodies. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope. Preferred polyclonal and monoclonal antibody compositions are ones that have been selected for antibodies directed against a protein of the invention. Particularly preferred polyclonal and monoclonal antibody preparations are ones that contain only antibodies directed against a marker protein or fragment thereof.

Polyclonal antibodies can be prepared by immunizing a suitable subject with a protein of the invention as an immunogen. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. At an appropriate time after immunization, *e.g.*, when the specific antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies (mAb) by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497, the human B cell

hybridoma technique (see Kozbor *et al.*, 1983, *Immunol. Today* 4:72), the EBV-hybridoma technique (see Cole *et al.*, pp. 77-96 In *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., 1985) or trioma techniques. The technology for producing hybridomas is well known (see generally *Current Protocols in Immunology*, Coligan *et al.* ed., John Wiley & Sons, New York, 1994). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind the polypeptide of interest, *e.g.*, using a standard ELISA assay.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody directed against a protein of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with the polypeptide of interest. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275-1281; Griffiths *et al.* (1993) *EMBO J.* 12:725-734.

The invention also provides recombinant antibodies that specifically bind a protein of the invention. In preferred embodiments, the recombinant antibodies specifically binds a marker protein or fragment thereof. Recombinant antibodies include, but are not limited to, chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, single-chain antibodies and multi-specific antibodies. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. (See, *e.g.*, Cabilly *et al.*, U.S. Patent No. 4,816,567; and Boss *et al.*, U.S. Patent No. 4,816,397, which are incorporated herein by reference in their entirety.) Single-chain antibodies have an

antigen binding site and consist of a single polypeptide. They can be produced by techniques known in the art, for example using methods described in Ladner *et al.* U.S. Pat. No. 4,946,778 (which is incorporated herein by reference in its entirety); Bird *et al.*, (1988) *Science* 242:423-426; Whitlow *et al.*, (1991) *Methods in Enzymology* 2:1-9; 5 Whitlow *et al.*, (1991) *Methods in Enzymology* 2:97-105; and Huston *et al.*, (1991) *Methods in Enzymology Molecular Design and Modeling: Concepts and Applications* 203:46-88. Multi-specific antibodies are antibody molecules having at least two antigen-binding sites that specifically bind different antigens. Such molecules can be produced by techniques known in the art, for example using methods described in Segal, 10 U.S. Patent No. 4,676,980 (the disclosure of which is incorporated herein by reference in its entirety); Holliger *et al.*, (1993) *Proc. Natl. Acad. Sci. USA* 90:6444-6448; Whitlow *et al.*, (1994) *Protein Eng.* 7:1017-1026 and U.S. Pat. No. 6,121,424.

Humanized antibodies are antibody molecules from non-human species having one or more complementarity determining regions (CDRs) from the non-human 15 species and a framework region from a human immunoglobulin molecule. (See, *e.g.*, Queen, U.S. Patent No. 5,585,089, which is incorporated herein by reference in its entirety.) Humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 20 171,496; European Patent Application 173,494; PCT Publication No. WO 86/01533; U.S. Patent No. 4,816,567; European Patent Application 125,023; Better *et al.* (1988) *Science* 240:1041-1043; Liu *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu *et al.* (1987) *J. Immunol.* 139:3521-3526; Sun *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura *et al.* (1987) *Cancer Res.* 47:999-1005; Wood *et al.* (1985) 25 *Nature* 314:446-449; and Shaw *et al.* (1988) *J. Natl. Cancer Inst.* 80:1553-1559); Morrison (1985) *Science* 229:1202-1207; Oi *et al.* (1986) *Bio/Techniques* 4:214; U.S. Patent 5,225,539; Jones *et al.* (1986) *Nature* 321:552-525; Verhoeven *et al.* (1988) *Science* 239:1534; and Beidler *et al.* (1988) *J. Immunol.* 141:4053-4060.

More particularly, humanized antibodies can be produced, for example, 30 using transgenic mice which are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. The transgenic mice are immunized in the normal fashion with a selected antigen, *e.g.*, all or a portion of a polypeptide corresponding to a marker of the invention. Monoclonal

antibodies directed against the antigen can be obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995) *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, *e.g.*, U.S. Patent 5,625,126; U.S. Patent 5,633,425; U.S. Patent 5,569,825; U.S. Patent 5,661,016; and U.S. Patent 5,545,806. In addition, companies such as Abgenix, Inc. (Freemont, CA), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, *e.g.*, a murine antibody, is used to guide the selection of a completely human antibody recognizing the same epitope (Jespers *et al.*, 1994, *Bio/technology* 12:899-903).

The antibodies of the invention can be isolated after production (*e.g.*, from the blood or serum of the subject) or synthesis and further purified by well-known techniques. For example, IgG antibodies can be purified using protein A chromatography. Antibodies specific for a protein of the invention can be selected or (*e.g.*, partially purified) or purified by, *e.g.*, affinity chromatography. For example, a recombinantly expressed and purified (or partially purified) protein of the invention is produced as described herein, and covalently or non-covalently coupled to a solid support such as, for example, a chromatography column. The column can then be used to affinity purify antibodies specific for the proteins of the invention from a sample containing antibodies directed against a large number of different epitopes, thereby generating a substantially purified antibody composition, *i.e.*, one that is substantially free of contaminating antibodies. By a substantially purified antibody composition is meant, in this context, that the antibody sample contains at most only 30% (by dry weight) of contaminating antibodies directed against epitopes other than those of the desired protein of the invention, and preferably at most 20%, yet more preferably at most 10%, and most preferably at most 5% (by dry weight) of the sample is

contaminating antibodies. A purified antibody composition means that at least 99% of the antibodies in the composition are directed against the desired protein of the invention.

In a preferred embodiment, the substantially purified antibodies of the invention may specifically bind to a signal peptide, a secreted sequence, an extracellular domain, a transmembrane or a cytoplasmic domain or cytoplasmic membrane of a protein of the invention. In a particularly preferred embodiment, the substantially purified antibodies of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of a protein of the invention. In a more preferred embodiment, the substantially purified antibodies of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of a marker protein.

An antibody directed against a protein of the invention can be used to isolate the protein by standard techniques, such as affinity chromatography or immunoprecipitation. Moreover, such an antibody can be used to detect the marker protein or fragment thereof (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the level and pattern of expression of the marker. The antibodies can also be used diagnostically to monitor protein levels in tissues or body fluids (*e.g.* in a cervical-associated body fluid) as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by the use of an antibody derivative, which comprises an antibody of the invention coupled to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S or ^3H .

Antibodies of the invention may also be used as therapeutic agents in treating cancers. In a preferred embodiment, completely human antibodies of the invention are used for therapeutic treatment of human cancer patients, particularly those having an cervical cancer. In another preferred embodiment, antibodies that bind

5 specifically to a marker protein or fragment thereof are used for therapeutic treatment. Further, such therapeutic antibody may be an antibody derivative or immunotoxin comprising an antibody conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D,

10 ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate,

15 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*,

20 dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

The conjugated antibodies of the invention can be used for modifying a given biological response, for the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or

25 polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as ribosome-inhibiting protein (see Better et al., U.S. Patent No. 6,146,631, the disclosure of which is incorporated herein in its entirety), abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, .alpha.-interferon, .beta.-interferon, nerve growth factor, platelet derived growth factor,

30 tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophase colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, *e.g.*, Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug
5 Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in
10 *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.*, 62:119-58 (1982).

Accordingly, in one aspect, the invention provides substantially purified antibodies, antibody fragments and derivatives, all of which specifically bind to a
15 protein of the invention and preferably, a marker protein. In various embodiments, the substantially purified antibodies of the invention, or fragments or derivatives thereof, can be human, non-human, chimeric and/or humanized antibodies. In another aspect, the invention provides non-human antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein.
20 Such non-human antibodies can be goat, mouse, sheep, horse, chicken, rabbit, or rat antibodies. Alternatively, the non-human antibodies of the invention can be chimeric and/or humanized antibodies. In addition, the non-human antibodies of the invention can be polyclonal antibodies or monoclonal antibodies. In still a further aspect, the invention provides monoclonal antibodies, antibody fragments and derivatives, all of
25 which specifically bind to a protein of the invention and preferably, a marker protein. The monoclonal antibodies can be human, humanized, chimeric and/or non-human antibodies.

The invention also provides a kit containing an antibody of the invention conjugated to a detectable substance, and instructions for use. Still another aspect of the
30 invention is a pharmaceutical composition comprising an antibody of the invention. In one embodiment, the pharmaceutical composition comprises an antibody of the invention and a pharmaceutically acceptable carrier.

III. Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding a marker protein (or a portion of such a protein). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, namely expression vectors, are capable of directing the expression of genes to which they are operably linked. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids (vectors). However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell. This means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, *Methods in Enzymology: Gene Expression Technology* vol.185, Academic Press, San Diego, CA (1991). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell and

those which direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein.

The recombinant expression vectors of the invention can be designed for expression of a marker protein or a segment thereof in prokaryotic (*e.g.*, *E. coli*) or eukaryotic cells (*e.g.*, insect cells {using baculovirus expression vectors}, yeast cells or mammalian cells). Suitable host cells are discussed further in Goeddel, *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson, 1988, *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann *et al.*, 1988, *Gene* 69:301-315) and pET 11d (Studier *et al.*, p. 60-89, In *Gene Expression Technology: Methods in Enzymology* vol.185, Academic Press, San Diego, CA, 1991). Target gene expression from the pTrc vector relies on host RNA

polymerase transcription from a hybrid trp-lac fusion promoter. Target gene expression from the pET 11d vector relies on transcription from a T7 gn10-lac fusion promoter mediated by a co-expressed viral RNA polymerase (T7 gn1). This viral polymerase is supplied by host strains BL21(DE3) or HMS174(DE3) from a resident prophage
5 harboring a T7 gn1 gene under the transcriptional control of the lacUV 5 promoter.

One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein (Gottesman, p. 119-128, In *Gene Expression Technology: Methods in Enzymology* vol. 185, Academic Press, San Diego, CA, 1990. Another
10 strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada *et al.*, 1992, *Nucleic Acids Res.* 20:2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

15 In another embodiment, the expression vector is a yeast expression vector. Examples of vectors for expression in yeast *S. cerevisiae* include pYepSec1 (Baldari *et al.*, 1987, *EMBO J.* 6:229-234), pMFa (Kurjan and Herskowitz, 1982, *Cell* 30:933-943), pJRY88 (Schultz *et al.*, 1987, *Gene* 54:113-123), pYES2 (Invitrogen Corporation, San Diego, CA), and pPicZ (Invitrogen Corp, San Diego, CA).

20 Alternatively, the expression vector is a baculovirus expression vector. Baculovirus vectors available for expression of proteins in cultured insect cells (*e.g.*, Sf 9 cells) include the pAc series (Smith *et al.*, 1983, *Mol. Cell Biol.* 3:2156-2165) and the pVL series (Lucklow and Summers, 1989, *Virology* 170:31-39).

In yet another embodiment, a nucleic acid of the invention is expressed in
25 mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, 1987, *Nature* 329:840) and pMT2PC (Kaufman *et al.*, 1987, *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2,
30 cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook *et al.*, *supra*.

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (e.g., tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert *et al.*, 1987, *Genes Dev.* 1:268-277), lymphoid-specific promoters (Calame and Eaton, 1988, *Adv. Immunol.* 43:235-275), in particular promoters of T cell receptors (Winoto and Baltimore, 1989, *EMBO J.* 8:729-733) and immunoglobulins (Banerji *et al.*, 1983, *Cell* 33:729-740; Queen and Baltimore, 1983, *Cell* 33:741-748), neuron-specific promoters (e.g., the neurofilament promoter; Byrne and Ruddle, 1989, *Proc. Natl. Acad. Sci. USA* 86:5473-5477), pancreas-specific promoters (Edlund *et al.*, 1985, *Science* 230:912-916), and mammary gland-specific promoters (e.g., milk whey promoter; U.S. Patent No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, for example the murine hox promoters (Kessel and Gruss, 1990, *Science* 249:374-379) and the α -fetoprotein promoter (Camper and Tilghman, 1989, *Genes Dev.* 3:537-546).

The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operably linked to a regulatory sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to the mRNA encoding a polypeptide of the invention. Regulatory sequences operably linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue-specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid, or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes see Weintraub *et al.*, 1986, *Trends in Genetics*, Vol. 1(1).

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential
5 progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic (*e.g.*, *E. coli*) or eukaryotic cell (*e.g.*,
10 insect cells, yeast or mammalian cells).

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid into a host cell, including calcium
15 phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*supra*), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells
20 may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (*e.g.*, for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Cells stably transfected with the introduced nucleic acid
25 can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce a marker protein or a segment thereof. Accordingly, the invention further provides methods for producing a marker protein or a segment
30 thereof using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of the invention (into which a recombinant expression vector encoding a marker protein or a segment thereof has been introduced) in a suitable medium such that the is produced. In another embodiment, the method further

comprises isolating the marker protein or a segment thereof from the medium or the host cell.

The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which a sequences encoding a marker protein or a segment thereof have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous sequences encoding a marker protein of the invention have been introduced into their genome or homologous recombinant animals in which endogenous gene(s) encoding a marker protein have been altered. Such animals are useful for studying the function and/or activity of the marker protein and for identifying and/or evaluating modulators of marker protein. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, an "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

A transgenic animal of the invention can be created by introducing a nucleic acid encoding a marker protein into the male pronuclei of a fertilized oocyte, *e.g.*, by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to the transgene to direct expression of the polypeptide of the invention to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Patent No.

4,873,191 and in Hogan, *Manipulating the Mouse Embryo*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986. Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the transgene in its genome and/or expression of mRNA
5 encoding the transgene in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying the transgene can further be bred to other transgenic animals carrying other transgenes.

To create an homologous recombinant animal, a vector is prepared which
10 contains at least a portion of a gene encoding a marker protein into which a deletion, addition or substitution has been introduced to thereby alter, *e.g.*, functionally disrupt, the gene. In a preferred embodiment, the vector is designed such that, upon homologous recombination, the endogenous gene is functionally disrupted (*i.e.*, no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the vector
15 can be designed such that, upon homologous recombination, the endogenous gene is mutated or otherwise altered but still encodes functional protein (*e.g.*, the upstream regulatory region can be altered to thereby alter the expression of the endogenous protein). In the homologous recombination vector, the altered portion of the gene is flanked at its 5' and 3' ends by additional nucleic acid of the gene to allow for
20 homologous recombination to occur between the exogenous gene carried by the vector and an endogenous gene in an embryonic stem cell. The additional flanking nucleic acid sequences are of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (see, *e.g.*, Thomas and Capecchi, 1987, *Cell* 51:503 for a
25 description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced gene has homologously recombined with the endogenous gene are selected (see, *e.g.*, Li *et al.*, 1992, *Cell* 69:915). The selected cells are then injected into a blastocyst of an animal (*e.g.*, a mouse) to form aggregation chimeras (see, *e.g.*, Bradley,
30 *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, Robertson, Ed., IRL, Oxford, 1987, pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed

animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley (1991) *Current Opinion in Bio/Technology* 2:823-829 and in PCT Publication NOS. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169.

In another embodiment, transgenic non-human animals can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, e.g., Lakso *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman *et al.*, 1991, *Science* 251:1351-1355). If a *cre/loxP* recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the *Cre* recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmot *et al.* (1997) *Nature* 385:810-813 and PCT Publication NOS. WO 97/07668 and WO 97/07669.

IV. Pharmaceutical Compositions

The nucleic acid molecules, polypeptides, and antibodies (also referred to herein as "active compounds") of the invention can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is

contemplated. Supplementary active compounds can also be incorporated into the compositions.

The invention includes methods for preparing pharmaceutical compositions for modulating the expression or activity of a marker nucleic acid or protein. Such methods comprise formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a marker nucleic acid or protein. Such compositions can further include additional active agents. Thus, the invention further includes methods for preparing a pharmaceutical composition by formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a marker nucleic acid or protein and one or more additional active compounds.

The invention also provides methods (also referred to herein as "screening assays") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, peptoids, small molecules or other drugs) which (a) bind to the marker, or (b) have a modulatory (*e.g.*, stimulatory or inhibitory) effect on the activity of the marker or, more specifically, (c) have a modulatory effect on the interactions of the marker with one or more of its natural substrates (*e.g.*, peptide, protein, hormone, co-factor, or nucleic acid), or (d) have a modulatory effect on the expression of the marker. Such assays typically comprise a reaction between the marker and one or more assay components. The other components may be either the test compound itself, or a combination of test compound and a natural binding partner of the marker.

The test compounds of the present invention may be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. Test compounds may also be obtained by any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; peptoid libraries (libraries of molecules having the functionalities of peptides, but with a novel, non-peptide backbone which are resistant to enzymatic degradation but which nevertheless remain bioactive; see, *e.g.*, Zuckermann *et al.*, 1994, *J. Med. Chem.* 37:2678-85); spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library and peptoid library approaches are limited to peptide libraries, while

the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, 1997, *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann *et al.* (1994). *J. Med. Chem.* 37:2678; Cho *et al.* (1993) *Science* 261:1303; Carrell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop *et al.* (1994) *J. Med. Chem.* 37:1233.

Libraries of compounds may be presented in solution (e.g., Houghten, 1992, *Biotechniques* 13:412-421), or on beads (Lam, 1991, *Nature* 354:82-84), chips (Fodor, 1993, *Nature* 364:555-556), bacteria and/or spores, (Ladner, USP 5,223,409), plasmids (Cull *et al.*, 1992, *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith, 1990, *Science* 249:386-390; Devlin, 1990, *Science* 249:404-406; Cwirla *et al.*, 1990, *Proc. Natl. Acad. Sci.* 87:6378-6382; Felici, 1991, *J. Mol. Biol.* 222:301-310; Ladner, *supra.*).

In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a protein encoded by or corresponding to a marker or biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to a protein encoded by or corresponding to a marker or biologically active portion thereof. Determining the ability of the test compound to directly bind to a protein can be accomplished, for example, by coupling the compound with a radioisotope or enzymatic label such that binding of the compound to the marker can be determined by detecting the labeled marker compound in a complex. For example, compounds (e.g., marker substrates) can be labeled with ^{125}I , ^{35}S , ^{14}C , or ^3H , either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, assay components can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

In another embodiment, the invention provides assays for screening candidate or test compounds which modulate the expression of a marker or the activity of a protein encoded by or corresponding to a marker, or a biologically active portion

thereof. In all likelihood, the protein encoded by or corresponding to the marker can, *in vivo*, interact with one or more molecules, such as but not limited to, peptides, proteins, hormones, cofactors and nucleic acids. For the purposes of this discussion, such cellular and extracellular molecules are referred to herein as "binding partners" or marker
5 "substrate".

One necessary embodiment of the invention in order to facilitate such screening is the use of a protein encoded by or corresponding to marker to identify the protein's natural *in vivo* binding partners. There are many ways to accomplish this which are known to one skilled in the art. One example is the use of the marker protein
10 as "bait protein" in a two-hybrid assay or three-hybrid assay (see, *e.g.*, U.S. Patent No. 5,283,317; Zervos *et al*, 1993, *Cell* 72:223-232; Madura *et al*, 1993, *J. Biol. Chem.* 268:12046-12054; Bartel *et al*, 1993, *Biotechniques* 14:920-924; Iwabuchi *et al*, 1993 *Oncogene* 8:1693-1696; Brent WO94/10300) in order to identify other proteins which bind to or interact with the marker (binding partners) and, therefore, are possibly
15 involved in the natural function of the marker. Such marker binding partners are also likely to be involved in the propagation of signals by the marker protein or downstream elements of a marker protein-mediated signaling pathway. Alternatively, such marker protein binding partners may also be found to be inhibitors of the marker protein.

The two-hybrid system is based on the modular nature of most
20 transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that encodes a marker protein fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g.*, GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is
25 fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming a marker-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) which is operably linked to a transcriptional regulatory site responsive to
30 the transcription factor. Expression of the reporter gene can be readily detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the marker protein.

In a further embodiment, assays may be devised through the use of the invention for the purpose of identifying compounds which modulate (*e.g.*, affect either positively or negatively) interactions between a marker protein and its substrates and/or binding partners. Such compounds can include, but are not limited to, molecules such as antibodies, peptides, hormones, oligonucleotides, nucleic acids, and analogs thereof. Such compounds may also be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. The preferred assay components for use in this embodiment is an cervical cancer marker protein identified herein, the known binding partner and/or substrate of same, and the test compound. Test compounds can be supplied from any source.

The basic principle of the assay systems used to identify compounds that interfere with the interaction between the marker protein and its binding partner involves preparing a reaction mixture containing the marker protein and its binding partner under conditions and for a time sufficient to allow the two products to interact and bind, thus forming a complex. In order to test an agent for inhibitory activity, the reaction mixture is prepared in the presence and absence of the test compound. The test compound can be initially included in the reaction mixture, or can be added at a time subsequent to the addition of the marker protein and its binding partner. Control reaction mixtures are incubated without the test compound or with a placebo. The formation of any complexes between the marker protein and its binding partner is then detected. The formation of a complex in the control reaction, but less or no such formation in the reaction mixture containing the test compound, indicates that the compound interferes with the interaction of the marker protein and its binding partner. Conversely, the formation of more complex in the presence of compound than in the control reaction indicates that the compound may enhance interaction of the marker protein and its binding partner.

The assay for compounds that interfere with the interaction of the marker protein with its binding partner may be conducted in a heterogeneous or homogeneous format. Heterogeneous assays involve anchoring either the marker protein or its binding partner onto a solid phase and detecting complexes anchored to the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be varied to obtain different information about the compounds being tested. For example, test compounds

that interfere with the interaction between the marker proteins and the binding partners (e.g., by competition) can be identified by conducting the reaction in the presence of the test substance, *i.e.*, by adding the test substance to the reaction mixture prior to or simultaneously with the marker and its interactive binding partner. Alternatively, test compounds that disrupt preformed complexes, *e.g.*, compounds with higher binding constants that displace one of the components from the complex, can be tested by adding the test compound to the reaction mixture after complexes have been formed. The various formats are briefly described below.

In a heterogeneous assay system, either the marker protein or its binding partner is anchored onto a solid surface or matrix, while the other corresponding non-anchored component may be labeled, either directly or indirectly. In practice, microtitre plates are often utilized for this approach. The anchored species can be immobilized by a number of methods, either non-covalent or covalent, that are typically well known to one who practices the art. Non-covalent attachment can often be accomplished simply by coating the solid surface with a solution of the marker protein or its binding partner and drying. Alternatively, an immobilized antibody specific for the assay component to be anchored can be used for this purpose. Such surfaces can often be prepared in advance and stored.

In related embodiments, a fusion protein can be provided which adds a domain that allows one or both of the assay components to be anchored to a matrix. For example, glutathione-S-transferase/marker fusion proteins or glutathione-S-transferase/binding partner can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtiter plates, which are then combined with the test compound or the test compound and either the non-adsorbed marker or its binding partner, and the mixture incubated under conditions conducive to complex formation (*e.g.*, physiological conditions). Following incubation, the beads or microtiter plate wells are washed to remove any unbound assay components, the immobilized complex assessed either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of marker binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either a marker protein or a marker protein binding partner can be immobilized utilizing conjugation of biotin and

streptavidin. Biotinylated marker protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the
5 protein-immobilized surfaces can be prepared in advance and stored.

In order to conduct the assay, the corresponding partner of the immobilized assay component is exposed to the coated surface with or without the test compound. After the reaction is complete, unreacted assay components are removed (*e.g.*, by washing) and any complexes formed will remain immobilized on the solid
10 surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the non-immobilized component is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the non-immobilized component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; *e.g.*, using a labeled antibody specific for
15 the initially non-immobilized species (the antibody, in turn, can be directly labeled or indirectly labeled with, *e.g.*, a labeled anti-Ig antibody). Depending upon the order of addition of reaction components, test compounds which modulate (inhibit or enhance) complex formation or which disrupt preformed complexes can be detected.

In an alternate embodiment of the invention, a homogeneous assay may
20 be used. This is typically a reaction, analogous to those mentioned above, which is conducted in a liquid phase in the presence or absence of the test compound. The formed complexes are then separated from unreacted components, and the amount of complex formed is determined. As mentioned for heterogeneous assay systems, the order of addition of reactants to the liquid phase can yield information about which test
25 compounds modulate (inhibit or enhance) complex formation and which disrupt preformed complexes.

In such a homogeneous assay, the reaction products may be separated from unreacted assay components by any of a number of standard techniques, including but not limited to: differential centrifugation, chromatography, electrophoresis and
30 immunoprecipitation. In differential centrifugation, complexes of molecules may be separated from uncomplexed molecules through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., *Trends Biochem Sci* 1993

Aug;18(8):284-7). Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger
5 complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively different charge properties of the complex as compared to the uncomplexed molecules may be exploited to differentially separate the complex from the remaining individual reactants, for example through the use of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to
10 one skilled in the art (see, *e.g.*, Heegaard, 1998, *J Mol. Recognit.* 11:141-148; Hage and Tweed, 1997, *J. Chromatogr. B. Biomed. Sci. Appl.*, 699:499-525). Gel electrophoresis may also be employed to separate complexed molecules from unbound species (see, *e.g.*, Ausubel *et al* (eds.), In: *Current Protocols in Molecular Biology*, J. Wiley & Sons, New York, 1999). In this technique, protein or nucleic acid complexes are separated based on
15 size or charge, for example. In order to maintain the binding interaction during the electrophoretic process, nondenaturing gels in the absence of reducing agent are typically preferred, but conditions appropriate to the particular interactants will be well known to one skilled in the art. Immunoprecipitation is another common technique utilized for the isolation of a protein-protein complex from solution (see, *e.g.*, Ausubel *et al* (eds.), In: *Current Protocols in Molecular Biology*, J. Wiley & Sons, New York,
20 1999). In this technique, all proteins binding to an antibody specific to one of the binding molecules are precipitated from solution by conjugating the antibody to a polymer bead that may be readily collected by centrifugation. The bound assay components are released from the beads (through a specific proteolysis event or other technique well known in the art which will not disturb the protein-protein interaction in the complex), and a second immunoprecipitation step is performed, this time utilizing antibodies specific for the correspondingly different interacting assay component. In this manner, only formed complexes should remain attached to the beads. Variations in complex formation in both the presence and the absence of a test compound can be
30 compared, thus offering information about the ability of the compound to modulate interactions between the marker protein and its binding partner.

Also within the scope of the present invention are methods for direct detection of interactions between the marker protein and its natural binding partner and/or a test compound in a homogeneous or heterogeneous assay system without further sample manipulation. For example, the technique of fluorescence energy transfer may be utilized (see, *e.g.*, Lakowicz *et al.*, U.S. Patent No. 5,631,169; Stavrianopoulos *et al.*, U.S. Patent No. 4,868,103). Generally, this technique involves the addition of a fluorophore label on a first 'donor' molecule (*e.g.*, marker or test compound) such that its emitted fluorescent energy will be absorbed by a fluorescent label on a second, 'acceptor' molecule (*e.g.*, marker or test compound), which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (*e.g.*, using a fluorimeter). A test substance which either enhances or hinders participation of one of the species in the preformed complex will result in the generation of a signal variant to that of background. In this way, test substances that modulate interactions between a marker and its binding partner can be identified in controlled assays.

In another embodiment, modulators of marker expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of marker mRNA or protein in the cell, is determined. The level of expression of marker mRNA or protein in the presence of the candidate compound is compared to the level of expression of marker mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of marker expression based on this comparison. For example, when expression of marker mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of marker mRNA or protein expression. Conversely, when expression of marker mRNA or protein is less (statistically significantly less) in the presence of the candidate compound

than in its absence, the candidate compound is identified as an inhibitor of marker mRNA or protein expression. The level of marker mRNA or protein expression in the cells can be determined by methods described herein for detecting marker mRNA or protein.

5 In another aspect, the invention pertains to a combination of two or more of the assays described herein. For example, a modulating agent can be identified using a cell-based or a cell free assay, and the ability of the agent to modulate the activity of a marker protein can be further confirmed *in vivo*, *e.g.*, in a whole animal model for cellular transformation and/or tumorigenesis.

10 This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, a marker modulating agent, an antisense marker nucleic acid molecule, a marker-specific antibody, or a marker-binding
15 partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

20 It is understood that appropriate doses of small molecule agents and protein or polypeptide agents depends upon a number of factors within the knowledge of the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of these agents will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending upon the route by which the composition is to
25 be administered, if applicable, and the effect which the practitioner desires the agent to have upon the nucleic acid or polypeptide of the invention. Exemplary doses of a small molecule include milligram or microgram amounts per kilogram of subject or sample weight (*e.g.* about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1
30 microgram per kilogram to about 50 micrograms per kilogram). Exemplary doses of a protein or polypeptide include gram, milligram or microgram amounts per kilogram of subject or sample weight (*e.g.* about 1 microgram per kilogram to about 5 grams per kilogram, about 100 micrograms per kilogram to about 500 milligrams per kilogram, or

about 1 milligram per kilogram to about 50 milligrams per kilogram). It is furthermore understood that appropriate doses of one of these agents depend upon the potency of the agent with respect to the expression or activity to be modulated. Such appropriate doses can be determined using the assays described herein. When one or more of these agents
5 is to be administered to an animal (*e.g.* a human) in order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher can, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend
10 upon a variety of factors including the activity of the specific agent employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

A pharmaceutical composition of the invention is formulated to be
15 compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline
20 solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediamine-tetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with
25 acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the
30 extemporaneous preparation of sterile injectable solutions or dispersions. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL (BASF; Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy

syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

15 Sterile injectable solutions can be prepared by incorporating the active compound (e.g., a polypeptide or antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium, and then incorporating the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

25 Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed.

30 Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches, and the like can contain any of the following ingredients, or compounds of a similar nature: a

binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as
5 peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from a pressurized container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal
10 means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal
15 administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

20 In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid.
25 Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes having monoclonal antibodies incorporated therein or thereon) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled
30 in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the

subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

For antibodies, the preferred dosage is 0.1 mg/kg to 100 mg/kg of body weight (generally 10 mg/kg to 20 mg/kg). If the antibody is to act in the brain, a dosage of 50 mg/kg to 100 mg/kg is usually appropriate. Generally, partially human antibodies and fully human antibodies have a longer half-life within the human body than other antibodies. Accordingly, lower dosages and less frequent administration is often possible. Modifications such as lipidation can be used to stabilize antibodies and to enhance uptake and tissue penetration (*e.g.*, into the cervical epithelium). A method for lipidation of antibodies is described by Cruikshank *et al.* (1997) *J. Acquired Immune Deficiency Syndromes and Human Retrovirology* 14:193.

The invention also provides vaccine compositions for the prevention and/or treatment of cervical cancer. The invention provides cervical cancer vaccine compositions in which a protein of a marker of Table 1, or a combination of proteins of the markers of Table 1, are introduced into a subject in order to stimulate an immune response against the cervical cancer. The invention also provides cervical cancer vaccine compositions in which a gene expression construct, which expresses a marker or fragment of a marker identified in Table 1, is introduced into the subject such that a protein or fragment of a protein encoded by a marker of Table 1 is produced by transfected cells in the subject at a higher than normal level and elicits an immune response.

In one embodiment, a cervical cancer vaccine is provided and employed as an immunotherapeutic agent for the prevention of cervical cancer. In another embodiment, a cervical cancer vaccine is provided and employed as an immunotherapeutic agent for the treatment of cervical cancer.

By way of example, a cervical cancer vaccine comprised of the proteins of the markers of Table 1, may be employed for the prevention and/or treatment of cervical cancer in a subject by administering the vaccine by a variety of routes, *e.g.*, intradermally, subcutaneously, or intramuscularly. In addition, the cervical cancer

vaccine can be administered together with adjuvants and/or immunomodulators to boost the activity of the vaccine and the subject's response. In one embodiment, devices and/or compositions containing the vaccine, suitable for sustained or intermittent release could be, implanted in the body or topically applied thereto for the relatively slow
5 release of such materials into the body. The cervical cancer vaccine can be introduced along with immunomodulatory compounds, which can alter the type of immune response produced in order to produce a response which will be more effective in eliminating the cancer.

In another embodiment, a cervical cancer vaccine comprised of an
10 expression construct of the markers of Table 1, may be introduced by injection into muscle or by coating onto microprojectiles and using a device designed for the purpose to fire the projectiles at high speed into the skin. The cells of the subject will then express the protein(s) or fragments of proteins of the markers of Table 1 and induce an immune
15 response. In addition, the cervical cancer vaccine may be introduced along with expression constructs for immunomodulatory molecules, such as cytokines, which may increase the immune response or modulate the type of immune response produced in order to produce a response which will be more effective in eliminating the cancer.

The marker nucleic acid molecules can be inserted into vectors and used
20 as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (U.S. Patent 5,328,470), or by stereotactic injection (see, *e.g.*, Chen *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which
25 the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.* retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

The pharmaceutical compositions can be included in a container, pack, or
30 dispenser together with instructions for administration.

V. Predictive Medicine

The present invention pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trails are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for determining the level of expression of one or more marker proteins or nucleic acids, in order to determine whether an individual is at risk of developing cervical cancer. Such assays can be used for prognostic or predictive purposes to thereby prophylactically treat an individual prior to the onset of the cancer.

Yet another aspect of the invention pertains to monitoring the influence of agents (*e.g.*, drugs or other compounds administered either to inhibit cervical cancer or to treat or prevent any other disorder {*i.e.* in order to understand any cervical carcinogenic effects that such treatment may have}) on the expression or activity of a marker of the invention in clinical trials. These and other agents are described in further detail in the following sections.

A. Diagnostic Assays

An exemplary method for detecting the presence or absence of a marker protein or nucleic acid in a biological sample involves obtaining a biological sample (*e.g.* a cervical-associated body fluid) from a test subject and contacting the biological sample with a compound or an agent capable of detecting the polypeptide or nucleic acid (*e.g.*, mRNA, genomic DNA, or cDNA). The detection methods of the invention can thus be used to detect mRNA, protein, cDNA, or genomic DNA, for example, in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of a marker protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of genomic DNA include Southern hybridizations. Furthermore, *in vivo* techniques for detection of a marker protein include introducing into a subject a labeled antibody directed against the protein or fragment thereof. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

A general principle of such diagnostic and prognostic assays involves preparing a sample or reaction mixture that may contain a marker, and a probe, under appropriate conditions and for a time sufficient to allow the marker and probe to interact and bind, thus forming a complex that can be removed and/or detected in the reaction mixture. These assays can be conducted in a variety of ways.

For example, one method to conduct such an assay would involve anchoring the marker or probe onto a solid phase support, also referred to as a substrate, and detecting target marker/probe complexes anchored on the solid phase at the end of the reaction. In one embodiment of such a method, a sample from a subject, which is to be assayed for presence and/or concentration of marker, can be anchored onto a carrier or solid phase support. In another embodiment, the reverse situation is possible, in which the probe can be anchored to a solid phase and a sample from a subject can be allowed to react as an unanchored component of the assay.

There are many established methods for anchoring assay components to a solid phase. These include, without limitation, marker or probe molecules which are immobilized through conjugation of biotin and streptavidin. Such biotinylated assay components can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the surfaces with immobilized assay components can be prepared in advance and stored.

Other suitable carriers or solid phase supports for such assays include any material capable of binding the class of molecule to which the marker or probe belongs. Well-known supports or carriers include, but are not limited to, glass, polystyrene, nylon, polypropylene, nylon, polyethylene, dextran, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

In order to conduct assays with the above mentioned approaches, the non-immobilized component is added to the solid phase upon which the second component is anchored. After the reaction is complete, uncomplexed components may be removed (*e.g.*, by washing) under conditions such that any complexes formed will remain immobilized upon the solid phase. The detection of marker/probe complexes anchored to the solid phase can be accomplished in a number of methods outlined herein.

In a preferred embodiment, the probe, when it is the unanchored assay component, can be labeled for the purpose of detection and readout of the assay, either directly or indirectly, with detectable labels discussed herein and which are well-known to one skilled in the art.

5 It is also possible to directly detect marker/probe complex formation without further manipulation or labeling of either component (marker or probe), for example by utilizing the technique of fluorescence energy transfer (see, for example, Lakowicz *et al.*, U.S. Patent No. 5,631,169; Stavrianopoulos, *et al.*, U.S. Patent No. 4,868,103). A fluorophore label on the first, 'donor' molecule is selected such that, upon
10 excitation with incident light of appropriate wavelength, its emitted fluorescent energy will be absorbed by a fluorescent label on a second 'acceptor' molecule, which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label
15 may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured
20 through standard fluorometric detection means well known in the art (*e.g.*, using a fluorimeter).

 In another embodiment, determination of the ability of a probe to recognize a marker can be accomplished without labeling either assay component (probe or marker) by utilizing a technology such as real-time Biomolecular Interaction Analysis
25 (BIA) (see, *e.g.*, Sjolander, S. and Urbaniczky, C., 1991, *Anal. Chem.* 63:2338-2345 and Szabo *et al.*, 1995, *Curr. Opin. Struct. Biol.* 5:699-705). As used herein, "BIA" or "surface plasmon resonance" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcore). Changes in the mass at the binding surface (indicative of a binding event) result in alterations of the refractive index
30 of light near the surface (the optical phenomenon of surface plasmon resonance (SPR)), resulting in a detectable signal which can be used as an indication of real-time reactions between biological molecules.

Alternatively, in another embodiment, analogous diagnostic and prognostic assays can be conducted with marker and probe as solutes in a liquid phase. In such an assay, the complexed marker and probe are separated from uncomplexed components by any of a number of standard techniques, including but not limited to:

5 differential centrifugation, chromatography, electrophoresis and immunoprecipitation. In differential centrifugation, marker/probe complexes may be separated from uncomplexed assay components through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., 1993, *Trends Biochem Sci.* 18(8):284-7).

10 Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively

15 different charge properties of the marker/probe complex as compared to the uncomplexed components may be exploited to differentiate the complex from uncomplexed components, for example through the utilization of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, e.g., Heegaard, N.H., 1998, *J. Mol. Recognit.* Winter 11(1-6):141-8; Hage, D.S., and Tweed, S.A. *J Chromatogr B Biomed Sci Appl* 1997 Oct 20 10;699(1-2):499-525). Gel electrophoresis may also be employed to separate complexed assay components from unbound components (see, e.g., Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, 1987-1999). In this

25 technique, protein or nucleic acid complexes are separated based on size or charge, for example. In order to maintain the binding interaction during the electrophoretic process, non-denaturing gel matrix materials and conditions in the absence of reducing agent are typically preferred. Appropriate conditions to the particular assay and components thereof will be well known to one skilled in the art.

In a particular embodiment, the level of marker mRNA can be

30 determined both by *in situ* and by *in vitro* formats in a biological sample using methods known in the art. The term "biological sample" is intended to include tissues, cells, biological fluids and isolates thereof, isolated from a subject, as well as tissues, cells and fluids present within a subject. Many expression detection methods use isolated RNA.

For *in vitro* methods, any RNA isolation technique that does not select against the isolation of mRNA can be utilized for the purification of RNA from cervical cells (see, *e.g.*, Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York 1987-1999). Additionally, large numbers of tissue samples can readily be
5 processed using techniques well known to those of skill in the art, such as, for example, the single-step RNA isolation process of Chomczynski (1989, U.S. Patent No. 4,843,155).

The isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or Northern analyses, polymerase chain
10 reaction analyses and probe arrays. One preferred diagnostic method for the detection of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to the mRNA encoded by the gene being detected. The nucleic acid probe can be, for example, a full-length cDNA, or a portion thereof, such as an oligonucleotide of at least 7, 15, 30, 50, 100, 250 or 500 nucleotides in length and
15 sufficient to specifically hybridize under stringent conditions to a mRNA or genomic DNA encoding a marker of the present invention. Other suitable probes for use in the diagnostic assays of the invention are described herein. Hybridization of an mRNA with the probe indicates that the marker in question is being expressed.

In one format, the mRNA is immobilized on a solid surface and contacted
20 with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative format, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in detecting the level
25 of mRNA encoded by the markers of the present invention.

An alternative method for determining the level of mRNA marker in a sample involves the process of nucleic acid amplification, *e.g.*, by rtPCR (the experimental embodiment set forth in Mullis, 1987, U.S. Patent No. 4,683,202), ligase chain reaction (Barany, 1991, *Proc. Natl. Acad. Sci. USA*, 88:189-193), self sustained
30 sequence replication (Guatelli *et al.*, 1990, *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh *et al.*, 1989, *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi *et al.*, 1988, *Bio/Technology* 6:1197), rolling circle replication (Lizardi *et al.*, U.S. Patent No. 5,854,033) or any other nucleic acid

amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. As used herein, amplification primers are defined as being
5 a pair of nucleic acid molecules that can anneal to 5' or 3' regions of a gene (plus and minus strands, respectively, or vice-versa) and contain a short region in between. In general, amplification primers are from about 10 to 30 nucleotides in length and flank a region from about 50 to 200 nucleotides in length. Under appropriate conditions and with appropriate reagents, such primers permit the amplification of a nucleic acid
10 molecule comprising the nucleotide sequence flanked by the primers.

For *in situ* methods, mRNA does not need to be isolated from the cervical cells prior to detection. In such methods, a cell or tissue sample is prepared/processed using known histological methods. The sample is then immobilized on a support, typically a glass slide, and then contacted with a probe that can hybridize to mRNA that
15 encodes the marker.

As an alternative to making determinations based on the absolute expression level of the marker, determinations may be based on the normalized expression level of the marker. Expression levels are normalized by correcting the absolute expression level of a marker by comparing its expression to the expression of a
20 gene that is not a marker, *e.g.*, a housekeeping gene that is constitutively expressed. Suitable genes for normalization include housekeeping genes such as the actin gene, or epithelial cell-specific genes. This normalization allows the comparison of the expression level in one sample, *e.g.*, a patient sample, to another sample, *e.g.*, a non-cervical cancer sample, or between samples from different sources.

Alternatively, the expression level can be provided as a relative
25 expression level. To determine a relative expression level of a marker, the level of expression of the marker is determined for 10 or more samples of normal versus cancer cell isolates, preferably 50 or more samples, prior to the determination of the expression level for the sample in question. The mean expression level of each of the genes assayed
30 in the larger number of samples is determined and this is used as a baseline expression level for the marker. The expression level of the marker determined for the test sample (absolute level of expression) is then divided by the mean expression value obtained for that marker. This provides a relative expression level.

Preferably, the samples used in the baseline determination will be from cervical cancer or from non-cervical cancer cells of cervical tissue. The choice of the cell source is dependent on the use of the relative expression level. Using expression found in normal tissues as a mean expression score aids in validating whether the marker
5 assayed is cervical specific (versus normal cells). In addition, as more data is accumulated, the mean expression value can be revised, providing improved relative expression values based on accumulated data. Expression data from cervical cells provides a means for grading the severity of the cervical cancer state.

In another embodiment of the present invention, a marker protein is
10 detected. A preferred agent for detecting marker protein of the invention is an antibody capable of binding to such a protein or a fragment thereof, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment or derivative thereof (*e.g.*, Fab or F(ab')₂) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct
15 labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with
20 fluorescently labeled streptavidin.

Proteins from cervical cells can be isolated using techniques that are well known to those of skill in the art. The protein isolation methods employed can, for example, be such as those described in Harlow and Lane (Harlow and Lane, 1988, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring
25 Harbor, New York).

A variety of formats can be employed to determine whether a sample contains a protein that binds to a given antibody. Examples of such formats include, but are not limited to, enzyme immunoassay (EIA), radioimmunoassay (RIA), Western blot analysis and enzyme linked immunoabsorbant assay (ELISA). A skilled artisan can
30 readily adapt known protein/antibody detection methods for use in determining whether cervical cells express a marker of the present invention.

In one format, antibodies, or antibody fragments or derivatives, can be used in methods such as Western blots or immunofluorescence techniques to detect the expressed proteins. In such uses, it is generally preferable to immobilize either the antibody or proteins on a solid support. Suitable solid phase supports or carriers include
5 any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

One skilled in the art will know many other suitable carriers for binding antibody or antigen, and will be able to adapt such support for use with the present
10 invention. For example, protein isolated from cervical cells can be run on a polyacrylamide gel electrophoresis and immobilized onto a solid phase support such as nitrocellulose. The support can then be washed with suitable buffers followed by treatment with the detectably labeled antibody. The solid phase support can then be washed with the buffer a second time to remove unbound antibody. The amount of
15 bound label on the solid support can then be detected by conventional means.

The invention also encompasses kits for detecting the presence of a marker protein or nucleic acid in a biological sample (*e.g.*, cervical smear). Such kits can be used to determine if a subject is suffering from or is at increased risk of developing cervical cancer. For example, the kit can comprise a labeled compound or
20 agent capable of detecting a marker protein or nucleic acid in a biological sample and means for determining the amount of the protein or mRNA in the sample (*e.g.*, an antibody which binds the protein or a fragment thereof, or an oligonucleotide probe which binds to DNA or mRNA encoding the protein). Kits can also include instructions for interpreting the results obtained using the kit.

25 For antibody-based kits, the kit can comprise, for example: (1) a first antibody (*e.g.*, attached to a solid support) which binds to a marker protein; and, optionally, (2) a second, different antibody which binds to either the protein or the first antibody and is conjugated to a detectable label.

For oligonucleotide-based kits, the kit can comprise, for example: (1) an
30 oligonucleotide, *e.g.*, a detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a marker protein or (2) a pair of primers useful for amplifying a marker nucleic acid molecule. The kit can also comprise, *e.g.*, a buffering agent, a preservative, or a protein stabilizing agent. The kit can further comprise components

necessary for detecting the detectable label (*e.g.*, an enzyme or a substrate). The kit can also contain a control sample or a series of control samples which can be assayed and compared to the test sample. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package,
5 along with instructions for interpreting the results of the assays performed using the kit.

B. Pharmacogenomics

The markers of the invention are also useful as pharmacogenomic markers. As used herein, a "pharmacogenomic marker" is an objective biochemical
10 marker whose expression level correlates with a specific clinical drug response or susceptibility in a patient (see, *e.g.*, McLeod *et al.* (1999) *Eur. J. Cancer* 35(12): 1650-1652). The presence or quantity of the pharmacogenomic marker expression is related to the predicted response of the patient and more particularly the patient's tumor to therapy with a specific drug or class of drugs. By assessing the presence or quantity of
15 the expression of one or more pharmacogenomic markers in a patient, a drug therapy which is most appropriate for the patient, or which is predicted to have a greater degree of success, may be selected. For example, based on the presence or quantity of RNA or protein encoded by specific tumor markers in a patient, a drug or course of treatment may be selected that is optimized for the treatment of the specific tumor likely to be
20 present in the patient. The use of pharmacogenomic markers therefore permits selecting or designing the most appropriate treatment for each cancer patient without trying different drugs or regimes.

Another aspect of pharmacogenomics deals with genetic conditions that alters the way the body acts on drugs. These pharmacogenetic conditions can occur
25 either as rare defects or as polymorphisms. For example, glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common inherited enzymopathy in which the main clinical complication is hemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

As an illustrative embodiment, the activity of drug metabolizing enzymes
30 is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (*e.g.*, N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show

exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, a PM will show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

Thus, the level of expression of a marker of the invention in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual. In addition, pharmacogenetic studies can be used to apply genotyping of polymorphic alleles encoding drug-metabolizing enzymes to the identification of an individual's drug responsiveness phenotype. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a modulator of expression of a marker of the invention.

C. Monitoring Clinical Trials

Monitoring the influence of agents (*e.g.*, drug compounds) on the level of expression of a marker of the invention can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent to affect marker expression can be monitored in clinical trials of subjects receiving treatment for cervical cancer. In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) comprising the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of one or more selected markers of the invention in the pre-administration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the

level of expression of the marker(s) in the post-administration samples; (v) comparing the level of expression of the marker(s) in the pre-administration sample with the level of expression of the marker(s) in the post-administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example,

5 increased expression of the marker gene(s) during the course of treatment may indicate ineffective dosage and the desirability of increasing the dosage. Conversely, decreased expression of the marker gene(s) may indicate efficacious treatment and no need to change dosage.

10 D. Electronic Apparatus Readable Media and Arrays

Electronic apparatus readable media comprising a marker of the present invention is also provided. As used herein, "electronic apparatus readable media" refers to any suitable medium for storing, holding or containing data or information that can be read and accessed directly by an electronic apparatus. Such media can include, but are

15 not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as compact disc; electronic storage media such as RAM, ROM, EPROM, EEPROM and the like; general hard disks and hybrids of these categories such as magnetic/optical storage media. The medium is adapted or configured for having recorded thereon a marker of the present invention.

20 As used herein, the term "electronic apparatus" is intended to include any suitable computing or processing apparatus or other device configured or adapted for storing data or information. Examples of electronic apparatus suitable for use with the present invention include stand-alone computing apparatus; networks, including a local area network (LAN), a wide area network (WAN) Internet, Intranet, and Extranet;

25 electronic appliances such as a personal digital assistants (PDAs), cellular phone, pager and the like; and local and distributed processing systems.

As used herein, "recorded" refers to a process for storing or encoding information on the electronic apparatus readable medium. Those skilled in the art can readily adopt any of the presently known methods for recording information on known

30 media to generate manufactures comprising the markers of the present invention.

A variety of software programs and formats can be used to store the marker information of the present invention on the electronic apparatus readable medium. For example, the marker nucleic acid sequence can be represented in a word

processing text file, formatted in commercially-available software such as WordPerfect and MicroSoft Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like, as well as in other forms. Any number of data processor structuring formats (*e.g.*, text file or database) may be
5 employed in order to obtain or create a medium having recorded thereon the markers of the present invention.

By providing the markers of the invention in readable form, one can routinely access the marker sequence information for a variety of purposes. For example, one skilled in the art can use the nucleotide or amino acid sequences of the
10 present invention in readable form to compare a target sequence or target structural motif with the sequence information stored within the data storage means. Search means are used to identify fragments or regions of the sequences of the invention which match a particular target sequence or target motif.

The present invention therefore provides a medium for holding
15 instructions for performing a method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer, wherein the method comprises the steps of determining the presence or absence of a marker and based on the presence or absence of the marker, determining whether the subject has cervical cancer or a pre-disposition to cervical cancer and/or recommending a particular treatment for cervical cancer or pre-
20 cervical cancer condition.

The present invention further provides in an electronic system and/or in a network, a method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer associated with a marker wherein the method comprises the steps of determining the presence or absence of the marker, and based on the
25 presence or absence of the marker, determining whether the subject has cervical cancer or a pre-disposition to cervical cancer, and/or recommending a particular treatment for the cervical cancer or pre-cervical cancer condition. The method may further comprise the step of receiving phenotypic information associated with the subject and/or acquiring from a network phenotypic information associated with the subject.

30 The present invention also provides in a network, a method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer associated with a marker, said method comprising the steps of receiving information associated with the marker receiving phenotypic information associated with the subject,

acquiring information from the network corresponding to the marker and/or cervical cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has a cervical cancer or a pre-disposition to cervical cancer. The method may further comprise the step of

5 recommending a particular treatment for the cervical cancer or pre-cervical cancer condition.

The present invention also provides a business method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer, said method comprising the steps of receiving information associated with the marker, receiving

10 phenotypic information associated with the subject, acquiring information from the network corresponding to the marker and/or cervical cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has cervical cancer or a pre-disposition to cervical cancer. The method may further comprise the step of recommending a particular treatment for the

15 cervical cancer or pre-cervical cancer condition.

The invention also includes an array comprising a marker of the present invention. The array can be used to assay expression of one or more genes in the array. In one embodiment, the array can be used to assay gene expression in a tissue to ascertain tissue specificity of genes in the array. In this manner, up to about 7600 genes

20 can be simultaneously assayed for expression. This allows a profile to be developed showing a battery of genes specifically expressed in one or more tissues.

In addition to such qualitative determination, the invention allows the quantitation of gene expression. Thus, not only tissue specificity, but also the level of expression of a battery of genes in the tissue is ascertainable. Thus, genes can be

25 grouped on the basis of their tissue expression *per se* and level of expression in that tissue. This is useful, for example, in ascertaining the relationship of gene expression between or among tissues. Thus, one tissue can be perturbed and the effect on gene expression in a second tissue can be determined. In this context, the effect of one cell type on another cell type in response to a biological stimulus can be determined. Such a

30 determination is useful, for example, to know the effect of cell-cell interaction at the level of gene expression. If an agent is administered therapeutically to treat one cell type but has an undesirable effect on another cell type, the invention provides an assay to determine the molecular basis of the undesirable effect and thus provides the

opportunity to co-administer a counteracting agent or otherwise treat the undesired effect. Similarly, even within a single cell type, undesirable biological effects can be determined at the molecular level. Thus, the effects of an agent on expression of other than the target gene can be ascertained and counteracted.

5 In another embodiment, the array can be used to monitor the time course of expression of one or more genes in the array. This can occur in various biological contexts, as disclosed herein, for example development of cervical cancer, progression of cervical cancer, and processes, such a cellular transformation associated with cervical cancer.

10 The array is also useful for ascertaining the effect of the expression of a gene on the expression of other genes in the same cell or in different cells. This provides, for example, for a selection of alternate molecular targets for therapeutic intervention if the ultimate or downstream target cannot be regulated.

 The array is also useful for ascertaining differential expression patterns of
15 one or more genes in normal and abnormal cells. This provides a battery of genes that could serve as a molecular target for diagnosis or therapeutic intervention.

E. Surrogate Markers

 The markers of the invention may serve as surrogate markers for one or
20 more disorders or disease states or for conditions leading up to disease states, and in particular, cervical cancer. As used herein, a "surrogate marker" is an objective biochemical marker which correlates with the absence or presence of a disease or disorder, or with the progression of a disease or disorder (*e.g.*, with the presence or absence of a tumor). The presence or quantity of such markers is independent of the
25 disease. Therefore, these markers may serve to indicate whether a particular course of treatment is effective in lessening a disease state or disorder. Surrogate markers are of particular use when the presence or extent of a disease state or disorder is difficult to assess through standard methodologies (*e.g.*, early stage tumors), or when an assessment of disease progression is desired before a potentially dangerous clinical endpoint is
30 reached (*e.g.*, an assessment of cardiovascular disease may be made using cholesterol levels as a surrogate marker, and an analysis of HIV infection may be made using HIV RNA levels as a surrogate marker, well in advance of the undesirable clinical outcomes of myocardial infarction or fully-developed AIDS). Examples of the use of surrogate

markers in the art include: Koomen *et al.* (2000) *J. Mass. Spectrom.* 35: 258-264; and James (1994) *AIDS Treatment News Archive* 209.

The markers of the invention are also useful as pharmacodynamic markers. As used herein, a "pharmacodynamic marker" is an objective biochemical marker which correlates specifically with drug effects. The presence or quantity of a pharmacodynamic marker is not related to the disease state or disorder for which the drug is being administered; therefore, the presence or quantity of the marker is indicative of the presence or activity of the drug in a subject. For example, a pharmacodynamic marker may be indicative of the concentration of the drug in a biological tissue, in that the marker is either expressed or transcribed or not expressed or transcribed in that tissue in relationship to the level of the drug. In this fashion, the distribution or uptake of the drug may be monitored by the pharmacodynamic marker. Similarly, the presence or quantity of the pharmacodynamic marker may be related to the presence or quantity of the metabolic product of a drug, such that the presence or quantity of the marker is indicative of the relative breakdown rate of the drug *in vivo*. Pharmacodynamic markers are of particular use in increasing the sensitivity of detection of drug effects, particularly when the drug is administered in low doses. Since even a small amount of a drug may be sufficient to activate multiple rounds of marker transcription or expression, the amplified marker may be in a quantity which is more readily detectable than the drug itself. Also, the marker may be more easily detected due to the nature of the marker itself; for example, using the methods described herein, antibodies may be employed in an immune-based detection system for a protein marker, or marker-specific radiolabeled probes may be used to detect a mRNA marker. Furthermore, the use of a pharmacodynamic marker may offer mechanism-based prediction of risk due to drug treatment beyond the range of possible direct observations. Examples of the use of pharmacodynamic markers in the art include: Matsuda *et al.* US 6,033,862; Hattis *et al.* (1991) *Env. Health Perspect.* 90: 229-238; Schentag (1999) *Am. J. Health-Syst. Pharm.* 56 Suppl. 3: S21-S24; and Nicolau (1999) *Am. J. Health-Syst. Pharm.* 56 Suppl. 3: S16-S20.

VI. Experimental Protocol

A. Identification of clones

Cervical tumor specific cDNA clones were identified by transcription profiling using mRNA from 12 cervical tumors, 5 CIN III, 5 CIN I and 12 normal
5 cervical tissues. The subtracted libraries were constructed using mRNA from at least three independent normal ectocervix, B-lymphocytes, T-lymphocytes and other white blood cells (in activated and resting states) as drivers and four independent stage 1B cervical tumors or four independent CIN III cervical samples as testers. The top up-regulated clones in tumors or CIN III cervical tissues, as determined by proprietary
10 statistical analysis methods, were selected. The clusters in which the selected clones belong were blasted against both public and proprietary sequence databases in order to identify other EST sequences or clusters with significant overlap. Thus, contiguous EST sequences and/or clusters were assembled into full-length genes.

An identification of protein sequence corresponding to the clone was
15 accomplished by obtaining one of the following:

- a) a direct match between the protein sequence and at least one EST sequence in one of its 6 possible translations;
- b) a direct match between the nucleotide sequence for the mRNA corresponding to the protein sequence and at least one EST sequence;
- 20 c) a match between the protein sequence and a contiguous assembly (contig) of the EST sequences with other available EST sequences in the databases in one of its 6 possible translations; or
- d) a match between the nucleotide sequence for the mRNA corresponding to the protein sequence and a contiguous assembly of the EST sequences with other
25 available EST sequences in the databases in one of its 6 possible translations.

VII. Summary of the Data

Tables 1-3 list the markers obtained using the foregoing protocol. The tables provide the name of the gene corresponding to the marker ("Gene Name"), the
30 sequence listing identifier of the cDNA sequence of a nucleotide transcript encoded by or corresponding to the marker ("SEQ ID NO (nts)"), the sequence listing identifier of the amino acid sequence of a protein encoded by the nucleotide transcript ("SEQ ID NO

(AAs)'), and the location of the protein coding sequence within the cDNA sequence ("CDS").

Table 1 lists all of the markers of the invention which are over-expressed in cervical cancer cells compared to normal (*i.e.*, non-cancerous) cervical cells. Table 2
5 lists newly-identified nucleotide and amino acid sequences useful as cervical cancer markers. Table 3 lists newly-identified nucleotide sequences useful as cervical cancer markers.

Other Embodiments

10 Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims:

What is claimed:

1. An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 143, 145, 147, 149, 151,
5 167, 203, 217, 231, 233, 51, 65, 67, 68, 100, and 153.
2. A vector which contains the nucleic acid molecule of claim 1.
3. A host cell which contains the nucleic acid molecule of claim 1.
- 10 4. A method of assessing whether a patient is afflicted with cervical cancer, the method comprising comparing:
 - a) the level of expression of a marker in a patient sample, wherein the marker is selected from Table 1; and
 - 15 b) the normal level of expression of the marker in a control non-cervical cancer sample,wherein a significant increase in the level of expression of the marker in the patient sample and the normal level is an indication that the patient is afflicted with cervical cancer.
- 20 5. An isolated polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 143, 145, 147, 149, 151, 167, 203, 217, 231, and 233.
- 25 6. An antibody which selectively binds to the polypeptide of claim 5.
7. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 144, 146, 148, 150, 152, 168, 204, 218, 232, and 234.
- 30 8. An antibody which selectively binds to the polypeptide of claim 7.

SEQUENCE LISTING

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OF CERVICAL CANCER

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<212> PRT

<213> Homo sapiens

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Gln	Gly	Phe	Ser	Val	Glu	Leu	Glu	Ser	Glu	Ile	Ser	Thr	Thr	Ala	Asp
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<212> PRT

<213> Homo sapiens

<400> 4

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Ser Lys Lys Gln Lys Lys Lys Arg Lys Thr Ser Ser Ser Lys His Asp
35     40     45
Val Ser Ala His His Asp Leu Asn Ile Asp Gln Ser Gln Cys Asn Glu
50     55     60
Met Tyr Ile Asn Ser Ser Gln Arg Val Glu Ser Thr Val Ile Pro Glu
65     70     75     80
Ser Thr Ile Met Arg Thr Leu His Ser Gly Glu Ile Thr Ser His Glu
85     90     95
Gln Gly Phe Ser Val Glu Leu Glu Ser Glu Ile Ser Thr Thr Ala Asp
100    105    110
Asp Cys Ser Ser Glu Val Asn Gly Cys Ser Phe Val Met Arg Thr Gly
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Lys Pro Thr Asn Leu Leu Arg Glu Glu Glu Phe Gly Val Asp Asp Ser
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Tyr Ser Glu Gln Gly Ala Gln Asp Ser Pro Thr His Leu Glu Met Met
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Gln Leu Thr Ala Asn Leu Gln Gln Ala Arg Arg Glu Lys Asp Glu Thr
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Lys Lys Lys Glu Asp Phe Thr Met Gln Ile Ser Phe Leu Gln Glu Lys
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Gln	Leu	Glu	Asp	Leu	Val	Glu	Glu	Leu	Ser	Phe	Ser	Arg	Glu	Gln	Ile
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Lys Glu Lys	Glu Ile Thr Asn Leu	Glu Glu Gln Leu	Glu Gln Phe Arg		
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Glu Glu Leu	Glu Asn Lys Asn Glu	Glu Val Gln Gln	Leu His Met Gln		
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Gln Gly Phe Ser Val Glu Leu Glu Ser Glu Ile Ser Thr Thr Ala Asp
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Lys Pro Thr Asn Leu Leu Arg Glu Glu Glu Phe Gly Val Asp Asp Ser
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<212> PRT

<213> Homo sapiens

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Ser Lys Lys Gln Lys Lys Lys Arg Lys Thr Ser Ser Ser Lys His Asp
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 65          70          75          80
Ser Thr Ile Met Arg Thr Leu His Ser Gly Glu Ile Thr Ser His Glu
 85          90          95
Gln Gly Phe Ser Val Glu Leu Glu Ser Glu Ile Ser Thr Thr Ala Asp
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Lys Pro Thr Asn Leu Leu Arg Glu Glu Glu Phe Gly Val Asp Asp Ser
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Tyr Ser Glu Gln Gly Ala Gln Asp Ser Pro Thr His Leu Glu Met Met
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Gln Ile Gln Glu Lys Thr Asp Ile Ile Asp Arg Leu Glu Gln Glu Leu		1935
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Gln Leu Ala Asn His Leu Lys Glu Lys Thr Asp Lys Cys Ser Glu Leu		2110
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 Met Thr Phe Met Lys Asn Val Leu Lys Glu Thr Asn Phe Lys Met Asn
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<213> Homo sapiens

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<210> 12

<211> 414

<212> PRT

<213> Homo sapiens

<400> 12

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Met Arg Phe Lys Ser His Thr Val Glu Leu Arg Arg Pro Cys Ser Asp
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20           25           30
Ser Ala Leu Phe Leu Gly Val Arg Val Arg Ala Glu Glu Ala Gly Ala
35           40           45
Arg Val Gln Gln Asn Val Pro Ser Gly Thr Asp Thr Gly Asp Pro Gln
50           55           60
Ser Lys Pro Leu Gly Asp Trp Ala Ala Gly Thr Met Asp Pro Glu Ser
65           70           75           80
Ser Ile Phe Ile Glu Asp Ala Ile Lys Tyr Phe Lys Glu Lys Val Ser
85           90           95

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Thr	Gln	Asn	Leu	Leu	Leu	Leu	Leu	Thr	Asp	Asn	Glu	Ala	Trp	Asn	Gly
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Lys	Ala	Leu	Asp	Asn	Leu	Ala	Arg	Gln	Met	Ile	Met	Lys	Asp	Lys	Asn
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Leu	Ala	Asp	Gly	Val	Gln	Lys	Val	His	Lys	Gly	Thr	Thr	Ile	Ala	Asn
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Val	Val	Ser	Gly	Ser	Leu	Ser	Ile	Ser	Ser	Gly	Ile	Leu	Thr	Leu	Val
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Glu	Pro	Gly	Met	Glu	Leu	Gly	Ile	Thr	Ala	Ala	Leu	Thr	Gly	Ile	Thr
225					230				235						240
Ser	Ser	Thr	Ile	Asp	Tyr	Gly	Lys	Lys	Trp	Trp	Thr	Gln	Ala	Gln	Ala
			245					250					255		
His	Asp	Leu	Val	Ile	Lys	Ser	Leu	Asp	Lys	Leu	Lys	Glu	Val	Lys	Glu
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Phe	Leu	Gly	Glu	Asn	Ile	Ser	Asn	Phe	Leu	Ser	Leu	Ala	Gly	Asn	Thr
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Tyr	Gln	Leu	Thr	Arg	Gly	Ile	Gly	Lys	Asp	Ile	Arg	Ala	Leu	Arg	Arg
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			325					330					335		
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Asp	Val	Ala	Pro	Val	Ser	Phe	Phe	Leu	Val	Leu	Asp	Val	Val	Tyr	Leu
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Val	Tyr	Glu	Ser	Lys	His	Leu	His	Glu	Gly	Ala	Lys	Ser	Glu	Thr	Ala
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Glu	Glu	Leu	Lys	Lys	Val	Ala	Gln	Glu	Leu	Glu	Glu	Lys	Leu	Asn	Ile
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Leu	Asn	Asn	Asn	Tyr	Lys	Ile	Leu	Gln	Ala	Asp	Gln	Glu	Leu		
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<210> 13

<211> 2298

<212> DNA

<213> Homo sapiens

<400> 13

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<210> 14

<211> 331

<212> PRT

<213> Homo sapiens

<400> 14

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Glu Ala Trp Lys Arg Phe Val Thr Ala Ala Glu Leu Pro Arg Asp Glu
35          40          45
Ala Asp Ala Leu Tyr Glu Ala Leu Lys Lys Leu Arg Thr Tyr Ala Ala
50          55          60
Ile Glu Asp Glu Tyr Val Gln Gln Lys Asp Glu Gln Phe Arg Glu Trp
65          70          75          80
Phe Leu Lys Glu Phe Pro Gln Val Lys Arg Lys Ile Gln Glu Ser Ile
85          90          95
Glu Lys Leu Arg Ala Leu Ala Asn Gly Ile Glu Glu Val His Arg Gly
100          105          110
Cys Thr Ile Ser Asn Val Val Ser Ser Ser Thr Gly Ala Ala Ser Gly
115          120          125
Ile Met Ser Leu Ala Gly Leu Val Leu Ala Pro Phe Thr Ala Gly Thr
130          135          140
Ser Leu Ala Leu Thr Ala Ala Gly Val Gly Leu Gly Ala Ala Ser Ala
145          150          155          160
Val Thr Gly Ile Thr Thr Ser Ile Val Glu His Ser Tyr Thr Ser Ser
165          170          175
Ala Glu Ala Glu Ala Ser Arg Leu Thr Ala Thr Ser Ile Asp Arg Leu
180          185          190

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Lys Val Phe Lys Glu Val Met Arg Asp Ile Thr Pro Asn Leu Leu Ser
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 210 215 220
 Arg Ala Ile Arg Gln Ala Arg Ala Arg Ala Arg Leu Pro Val Thr Thr
 225 230 235 240
 Trp Arg Ile Ser Ala Gly Ser Gly Gly Gln Ala Glu Arg Thr Ile Ala
 245 250 255
 Gly Thr Thr Arg Ala Val Ser Arg Gly Ala Arg Ile Leu Ser Ala Thr
 260 265 270
 Thr Ser Gly Ile Phe Leu Ala Leu Asp Val Val Asn Leu Val Tyr Glu
 275 280 285
 Ser Lys His Leu His Glu Gly Ala Lys Ser Ala Ser Ala Glu Glu Leu
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<210> 15
 <211> 1316
 <212> DNA
 <213> Homo sapiens

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<210> 16
 <211> 265
 <212> PRT
 <213> Homo sapiens

<400> 16
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 20 25 30

Leu Lys Trp Pro Ser Ala Leu Pro Thr Ile Leu Gln Ile Ala Leu Ala
 35 40 45
 Phe Gly Leu Ala Ile Gly Thr Leu Ala Gln Ala Leu Gly Pro Val Ser
 50 55 60
 Gly Gly His Ile Asn Pro Ala Ile Thr Leu Ala Leu Leu Val Gly Asn
 65 70 75 80
 Gln Ile Ser Leu Leu Arg Ala Phe Phe Tyr Val Ala Ala Gln Leu Val
 85 90 95
 Gly Ala Ile Ala Gly Ala Gly Ile Leu Tyr Gly Val Ala Pro Leu Asn
 100 105 110
 Ala Arg Gly Asn Leu Ala Val Asn Ala Leu Asn Asn Asn Thr Thr Gln
 115 120 125
 Gly Gln Ala Met Val Val Glu Leu Ile Leu Thr Phe Gln Leu Ala Leu
 130 135 140
 Cys Ile Phe Ala Ser Thr Asp Ser Arg Arg Thr Ser Pro Val Gly Ser
 145 150 155 160
 Pro Ala Leu Ser Ile Gly Leu Ser Val Thr Leu Gly His Leu Val Gly
 165 170 175
 Ile Tyr Phe Thr Gly Cys Ser Met Asn Pro Ala Arg Ser Phe Gly Pro
 180 185 190
 Ala Val Val Met Asn Arg Phe Ser Pro Ala His Trp Val Phe Trp Val
 195 200 205
 Gly Pro Ile Val Gly Ala Val Leu Ala Ala Ile Leu Tyr Phe Tyr Leu
 210 215 220
 Leu Phe Pro Asn Ser Leu Ser Leu Ser Glu Arg Val Ala Ile Ile Lys
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 Gly Thr Tyr Glu Pro Asp Glu Asp Trp Glu Glu Gln Arg Glu Glu Arg
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 Lys Lys Thr Met Glu Leu Thr Thr Arg
 260 265

<210> 17

<211> 1258

<212> DNA

<213> Homo sapiens

<400> 17

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<210> 18
 <211> 22
 <212> PRT
 <213> Homo sapiens

<400> 18
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 Lys Leu Phe Asp Ser Tyr
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<210> 19
 <211> 983
 <212> DNA
 <213> Homo sapiens

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 <211> 180
 <212> PRT
 <213> Homo sapiens

<400> 20
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 35 40 45
 Asn Ser Glu Ala Cys Arg Asp Gly Leu Arg Ala Val Met Glu Cys Arg
 50 55 60
 Asn Val Thr His Leu Leu Gln Gln Glu Leu Thr Glu Ala Gln Lys Gly
 65 70 75 80
 Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys Asn His Thr Val Met
 85 90 95
 Ala Leu Met Ala Ser Leu Asp Ala Glu Lys Ala Gln Gly Gln Lys Lys
 100 105 110
 Val Glu Glu Leu Glu Gly Glu Ile Thr Thr Leu Asn His Lys Leu Gln
 115 120 125

Asp	Ala	Ser	Ala	Glu	Val	Glu	Arg	Leu	Arg	Arg	Glu	Asn	Gln	Val	Leu
130						135					140				
Ser	Val	Arg	Ile	Ala	Asp	Lys	Lys	Tyr	Tyr	Pro	Ser	Ser	Gln	Asp	Ser
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Ser	Ser	Ala	Ala	Ala	Pro	Gln	Leu	Leu	Ile	Val	Leu	Leu	Gly	Leu	Ser
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			180												

<210> 21
 <211> 4859
 <212> DNA
 <213> Homo sapiens

<400> 21

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<213> Homo sapiens

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<212> PRT

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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 50 55 60
 Leu Lys Asp Arg Thr Gly Phe Ala Val Ile His Asp Ala Ala Arg Ala
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 Gly Phe Leu Asp Thr Leu Gln Thr Leu Leu Glu Phe Gln Ala Asp Val
 85 90 95
 Asn Ile Glu Asp Asn Glu Gly Asn Leu Pro Leu His Leu Ala Ala Lys
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 Glu Gly His Leu Arg Val Val Glu Phe Leu Val Lys His Thr Ala Ser
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 <213> Homo sapiens

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<211> 184

<212> PRT

<213> Homo sapiens

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Arg His Ile Arg Lys Glu Glu Gly Ser Phe Gln Ser Cys Ser Phe Cys				
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<212> DNA

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<212> PRT

<213> Homo sapiens

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          20          25          30
Tyr Ser Tyr Ala Gly Asp Asn Ile Val Thr Ala Gln Ala Met Tyr Glu
          35          40          45
Gly Leu Trp Met Ser Cys Val Ser Gln Ser Thr Gly Gln Ile Gln Cys
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Lys Val Phe Asp Ser Leu Asn Leu Ser Ser Thr Leu Gln Ala Thr
          65          70          75          80
Arg Ala Leu Met Val Val Gly Ile Leu Leu Gly Val Ile Ala Ile Phe
          85          90          95
Val Ala Thr Val Gly Met Lys Cys Met Lys Cys Leu Glu Asp Asp Glu
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Leu Lys Thr Leu Gln Lys Leu Asp Glu Tyr Leu Asn Ser Pro Leu Pro
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Lys Phe Leu Asp Gly Asn Glu Met Thr Leu Ala Asp Cys Asn Leu Leu
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Pro Lys Leu His Ile Val Lys Val Val Ala Lys Lys Tyr Arg Asn Phe
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Tyr Asp Gly Lys Gly Val Gly Leu Gly Pro Gly Pro Met Gly Leu Met
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<210> 41

<211> 5064

<212> DNA

<213> Homo sapiens

<400> 41

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<210> 42

<211> 1224

<212> PRT

<213> Homo sapiens

<400> 42

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Ile Gln Leu Trp Asp Tyr Arg Met Cys Thr Leu Ile Asp Lys Phe Asp
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Glu His Asp Gly Pro Val Arg Gly Ile Asp Phe His Lys Gln Gln Pro
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Leu Phe Val Ser Gly Gly Asp Asp Tyr Lys Ile Lys Val Trp Asn Tyr
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Lys Leu Arg Arg Cys Leu Phe Thr Leu Leu Gly His Leu Asp Tyr Ile
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Arg Thr Thr Phe Phe His His Glu Tyr Pro Trp Ile Leu Ser Ala Ser
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Asp Asp Gln Thr Ile Arg Val Trp Asn Trp Gln Ser Arg Thr Cys Val
115          120          125
Cys Val Leu Thr Gly His Asn His Tyr Val Met Cys Ala Gln Phe His
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Pro Thr Glu Asp Leu Val Val Ser Ala Ser Leu Asp Gln Thr Val Arg
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Val Trp Asp Ile Ser Gly Leu Arg Lys Lys Asn Leu Ser Pro Gly Ala
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Val Glu Ser Asp Val Arg Gly Ile Thr Gly Val Asp Leu Phe Gly Thr
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Thr Asp Ala Val Val Lys His Val Leu Glu Gly His Asp Arg Gly Val
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Asp Asp Arg Gln Val Lys Ile Trp Arg Met Asn Glu Ser Lys Ala Trp
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Glu Val Asp Thr Cys Arg Gly His Tyr Asn Asn Val Ser Cys Ala Val
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Phe His Pro Arg Gln Glu Leu Ile Leu Ser Asn Ser Glu Asp Lys Ser
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Ile Arg Val Trp Asp Met Ser Lys Arg Thr Gly Val Gln Thr Phe Arg
275          280          285
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290          295          300
Leu Phe Ala Ala Gly His Asp Gly Gly Met Ile Val Phe Lys Leu Glu
305          310          315          320
Arg Glu Arg Pro Ala Tyr Ala Val His Gly Asn Met Leu His Tyr Val
325          330          335
Lys Asp Arg Phe Leu Arg Gln Leu Asp Phe Asn Ser Ser Lys Asp Val
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Ser Tyr Asn Pro Ala Glu Asn Ala Val Leu Leu Cys Thr Arg Ala Ser
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Ile	Arg	Thr	Leu	Asp	Leu	Pro	Ile	Tyr	Val	Thr	Arg	Val	Lys	Gly	Asn
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Asn	Val	Tyr	Cys	Leu	Asp	Arg	Glu	Cys	Arg	Pro	Arg	Val	Leu	Thr	Ile
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Asp	Glu	Val	Leu	His	Met	Val	Arg	Asn	Ala	Lys	Leu	Val	Gly	Gln	Ser
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Phe	Val	Lys	Asp	Glu	Lys	Thr	Arg	Phe	Ser	Leu	Ala	Leu	Glu	Cys	Gly
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Asn	Ile	Glu	Ile	Ala	Leu	Glu	Ala	Ala	Lys	Ala	Leu	Asp	Asp	Lys	Asn
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Cys	Trp	Glu	Lys	Leu	Gly	Glu	Val	Ala	Leu	Leu	Gln	Gly	Asn	His	Gln
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Ile	Val	Glu	Met	Cys	Tyr	Gln	Arg	Thr	Lys	Asn	Phe	Asp	Lys	Val	Ser
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Cys Pro Leu Ser Gly Ala Cys Tyr Ser Pro Glu Phe Lys Gly Gln Ile				
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<210> 43

<211> 266

<212> DNA

<213> Homo sapiens

<400> 43

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 Lys Pro Tyr Cys Asn His Pro Cys Tyr Ala Ala Met Phe Gly Pro Lys
 50 55 60
 Gly Phe Gly Arg Gly Gly Ala Glu Ser His Thr Phe Lys
 65 70 75

<210> 45
 <211> 2312
 <212> DNA
 <213> Homo sapiens

<400> 45
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 aacaccatag gtagaatgta aagcttgtct gatcgttcaa agcatgaaat ggatacttat 1980

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<210> 46

<211> 349

<212> PRT

<213> Homo sapiens

<400> 46

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 20          25          30
Cys Arg Cys Pro Asp Glu Pro Ala Pro Arg Cys Pro Ala Gly Val Ser
 35          40          45
Leu Val Leu Asp Gly Cys Gly Cys Cys Arg Val Cys Ala Lys Gln Leu
 50          55          60
Gly Glu Leu Cys Thr Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu
 65          70          75          80
Phe Cys Asp Phe Gly Ser Pro Ala Asn Arg Lys Ile Gly Val Cys Thr
 85          90          95
Ala Lys Asp Gly Ala Pro Cys Ile Phe Gly Gly Thr Val Tyr Arg Ser
 100          105          110
Gly Glu Ser Phe Gln Ser Ser Cys Lys Tyr Gln Cys Thr Cys Leu Asp
 115          120          125
Gly Ala Val Gly Cys Met Pro Leu Cys Ser Met Asp Val Arg Leu Pro
 130          135          140
Ser Pro Asp Cys Pro Phe Pro Arg Arg Val Lys Leu Pro Gly Lys Cys
 145          150          155          160
Cys Glu Glu Trp Val Cys Asp Glu Pro Lys Asp Gln Thr Val Val Gly
 165          170          175
Pro Ala Leu Ala Tyr Arg Leu Glu Asp Thr Phe Gly Pro Asp Pro
 180          185          190
Thr Met Ile Arg Ala Asn Cys Leu Val Gln Thr Thr Glu Trp Ser Ala
 195          200          205
Cys Ser Lys Thr Cys Gly Met Gly Ile Ser Thr Arg Val Thr Asn Asp
 210          215          220
Asn Ala Ser Cys Arg Leu Glu Lys Gln Ser Arg Leu Cys Met Val Arg
 225          230          235          240
Pro Cys Glu Ala Asp Leu Glu Glu Asn Ile Lys Lys Gly Lys Lys Cys
 245          250          255
Ile Arg Thr Pro Lys Ile Ser Lys Pro Ile Lys Phe Glu Leu Ser Gly
 260          265          270
Cys Thr Ser Met Lys Thr Tyr Arg Ala Lys Phe Cys Gly Val Cys Thr
 275          280          285
Asp Gly Arg Cys Cys Thr Pro His Arg Thr Thr Thr Leu Pro Val Glu
 290          295          300
Phe Lys Cys Pro Asp Gly Glu Val Met Lys Lys Asn Met Met Phe Ile
 305          310          315          320
Lys Thr Cys Ala Cys His Tyr Asn Cys Pro Gly Asp Asn Asp Ile Phe
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<210> 47
<211> 3025
<212> DNA
<213> Homo sapiens

<400> 47

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<210> 48

<211> 752

<212> PRT

<213> Homo sapiens

<400> 48

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			20					25					30		
Lys	Leu	Ala	Leu	Ala	Glu	Ala	Arg	Val	Gln	Glu	Glu	Glu	Gln	Lys	Ala
		35					40					45			
Thr	Arg	Leu	Glu	Lys	Glu	Leu	Gln	Thr	Gln	Thr	Thr	Lys	Phe	His	Gln
	50					55					60				
Asp	Gln	Asp	Thr	Ile	Met	Ala	Lys	Leu	Thr	Asn	Glu	Asp	Ser	Gln	Asn
65					70					75				80	
Arg	Gln	Leu	Gln	Gln	Lys	Leu	Ala	Ala	Leu	Ser	Arg	Gln	Ile	Asp	Glu
				85					90					95	
Leu	Glu	Glu	Thr	Asn	Arg	Ser	Leu	Arg	Lys	Ala	Glu	Glu	Glu	Glu	Gln
			100					105					110		
Asp	Ile	Lys	Glu	Lys	Ile	Ser	Lys	Gly	Glu	Tyr	Gly	Asn	Ala	Gly	Ile
		115					120					125			
Met	Ala	Glu	Val	Glu	Glu	Leu	Ile	Lys	Met	Glu	Glu	Gln	Cys	Arg	Asp
	130					135				140					
Leu	Asn	Lys	Arg	Leu	Glu	Arg	Glu	Thr	Leu	Gln	Ser	Lys	Asp	Phe	Lys
145					150					155					160
Leu	Glu	Val	Glu	Lys	Leu	Ser	Lys	Arg	Ile	Met	Ala	Leu	Glu	Lys	Leu
				165					170					175	
Glu	Asp	Ala	Phe	Asn	Lys	Ser	Lys	Gln	Glu	Cys	Tyr	Ser	Leu	Lys	Cys
		180					185						190		
Asn	Leu	Glu	Lys	Glu	Arg	Met	Thr	Thr	Lys	Gln	Leu	Ser	Gln	Glu	Leu
		195					200					205			
Glu	Ser	Leu	Lys	Val	Arg	Ile	Lys	Glu	Leu	Glu	Ala	Ile	Glu	Ser	Arg
	210				215						220				
Leu	Glu	Lys	Thr	Glu	Phe	Thr	Leu	Lys	Glu	Asp	Leu	Thr	Lys	Leu	Lys
225					230					235					240
Thr	Leu	Thr	Val	Met	Phe	Val	Asp	Glu	Arg	Lys	Thr	Met	Ser	Glu	Lys
				245					250					255	
Leu	Lys	Lys	Thr	Glu	Asp	Lys	Leu	Gln	Ala	Ala	Ser	Ser	Gln	Leu	Gln
			260				265						270		
Val	Glu	Gln	Asn	Lys	Val	Thr	Thr	Val	Thr	Glu	Lys	Leu	Ile	Glu	Glu
		275					280					285			
Thr	Lys	Arg	Ala	Leu	Lys	Ser	Lys	Thr	Asp	Val	Glu	Glu	Lys	Met	Tyr
	290					295				300					
Ser	Val	Thr	Lys	Glu	Arg	Asp	Asp	Leu	Lys	Asn	Lys	Leu	Lys	Ala	Glu
305					310					315					320
Glu	Glu	Lys	Gly	Asn	Asp	Leu	Leu	Ser	Arg	Val	Asn	Met	Leu	Lys	Asn
			325						330					335	
Arg	Leu	Gln	Ser	Leu	Glu	Ala	Ile	Glu	Lys	Asp	Phe	Leu	Lys	Asn	Lys
			340				345						350		
Leu	Asn	Gln	Asp	Ser	Gly	Lys	Ser	Thr	Thr	Ala	Leu	His	Gln	Glu	Asn
		355					360					365			
Asn	Lys	Ile	Lys	Glu	Leu	Ser	Gln	Glu	Val	Glu	Arg	Leu	Lys	Leu	Lys
	370					375				380					
Leu	Lys	Asp	Met	Lys	Ala	Ile	Glu	Asp	Asp	Leu	Met	Lys	Thr	Glu	Asp
385					390					395					400
Glu	Tyr	Glu	Thr	Leu	Glu	Arg	Arg	Tyr	Ala	Asn	Glu	Arg	Asp	Lys	Ala
				405					410					415	
Gln	Phe	Leu	Ser	Lys	Glu	Leu	Glu	His	Val	Lys	Met	Glu	Leu	Ala	Lys
			420					425					430		

Tyr Lys Leu Ala Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu Phe
 435 440 445
 Lys Arg Leu Gln Glu Glu Glu Ala Lys Ser Gly His Leu Ser Arg Glu
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 Val Asp Ala Leu Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu Asp
 465 470 475 480
 Leu Ile Cys His Leu Gln Gly Asp His Ser Val Cys Lys Lys Lys Leu
 485 490 495
 Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu Asn
 500 505 510
 Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu Arg
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 Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser Lys
 530 535 540
 Glu Val Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys Ser
 545 550 555 560
 Leu Ile Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu Glu
 565 570 575
 Ser Glu Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu Ser
 580 585 590
 Phe Lys Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu Trp
 595 600 605
 Ile Pro Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys Met
 610 615 620
 Gln Thr Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val Leu
 625 630 635 640
 Ser His Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp His
 645 650 655
 Val Gln Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu Ser
 660 665 670
 Pro His Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr Pro
 675 680 685
 Lys Gln Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val Lys
 690 695 700
 Ser Lys Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met Ser
 705 710 715 720
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 725 730 735
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 740 745 750

<210> 49

<211> 1480

<212> DNA

<213> Homo sapiens

<400> 49

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<210> 50

<211> 205

<212> PRT

<213> Homo sapiens

<400> 50

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Arg Asn Glu Asp Tyr Thr Ile His Val Gln Leu Asn Asp Tyr Val Asp
35        40        45
Ile Ile Cys Pro His Tyr Glu Asp His Ser Val Ala Asp Ala Ala Met
50        55        60
Glu Gln Tyr Ile Leu Tyr Leu Val Glu His Glu Tyr Gln Leu Cys
65        70        75        80
Gln Pro Gln Ser Lys Asp Gln Val Arg Trp Gln Cys Asn Arg Pro Ser
85        90        95
Ala Lys His Gly Pro Glu Lys Leu Ser Glu Lys Phe Gln Arg Phe Thr
100       105       110
Pro Phe Thr Leu Gly Lys Glu Phe Lys Glu Gly His Ser Tyr Tyr Tyr
115       120       125
Ile Ser Lys Pro Ile His Gln His Glu Asp Arg Cys Leu Arg Leu Lys
130       135       140
Val Thr Val Ser Gly Lys Ile Thr His Ser Pro Gln Ala His Val Asn
145       150       155       160
Pro Gln Glu Lys Arg Leu Ala Ala Asp Asp Pro Glu Val Arg Val Leu
165       170       175
His Ser Ile Gly His Ser Ala Ala Pro Arg Leu Phe Pro Leu Ala Trp
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Thr Val Leu Leu Leu Pro Leu Leu Leu Gln Thr Pro
195       200       205

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<210> 51

<211> 15952

<212> DNA

<213> Homo sapiens

<400> 51

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<212> PRT

<213> Homo sapiens

<400> 52

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20 25 30
Tyr Ala Ala Met Glu Gln Gly Leu Leu Pro Ala Gly Leu Gly Gln Ala
35 40 45
Leu Leu Glu Ala Gln Ala Ala Thr Gly Gly Leu Val Asp Leu Ala Arg
50 55 60
Gly Gln Leu Leu Pro Val Ser Lys Ala Leu Gln Gln Gly Leu Val Gly
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Leu Glu Leu Lys Glu Lys Leu Leu Ala Ala Glu Arg Ala Thr Thr Gly
85 90 95
Tyr Pro Asp Pro Tyr Gly Gly Glu Lys Leu Ala Leu Phe Gln Ala Ile
100 105 110
Gly Lys Glu Val Val Asp Arg Ala Leu Gly Gln Ser Trp Leu Glu Val
115 120 125
Gln Leu Ala Thr Gly Gly Leu Val Asp Pro Ala Gln Gly Val Leu Val
130 135 140
Ala Pro Glu Pro Ala Cys His Gln Gly Leu Leu Asp Arg Glu Thr Trp
145 150 155 160
His Lys Leu Ser Glu Leu Glu Pro Gly Thr Gly Asp Leu Arg Phe Leu
165 170 175
Asn Pro Asn Thr Leu Glu Arg Leu Thr Tyr His Gln Leu Leu Glu Arg
180 185 190
Cys Val Arg Ala Pro Gly Ser Gly Leu Ala Leu Leu Pro Leu Lys Ile
195 200 205

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Ala	Val	Thr	Gly	His	His	Asp	Pro	Phe	Ser	Gly	Ser	Gln	Ile	Pro	Leu
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Arg	Pro	Val	Ser	Leu	Trp	Glu	Leu	Leu	Phe	Ser	Glu	Ala	Ile	Ser	Ser
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Glu	Gln	Arg	Ala	Met	Leu	Ala	Gln	Gln	Tyr	Gln	Glu	Gly	Thr	Leu	Ser
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Val	Glu	Lys	Leu	Ala	Ala	Glu	Leu	Ser	Ala	Thr	Leu	Glu	Gln	Ala	Ala
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Gly	Glu	Leu	Leu	Lys	Ala	Glu	Ile	Ile	Asp	Gln	Asp	Leu	Tyr	Glu	Arg
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Glu	Ala	Leu	Arg	Ala	Ala	Val	Ile	Gly	Pro	Asp	Val	Phe	Ala	Lys	Leu
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Gln	Gln	Ile	Ser	Leu	Phe	Gln	Ala	Met	Gln	Lys	Gly	Leu	Ile	Val	Arg

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 Thr Gly Arg Ser Thr Thr Gln Glu Leu Met Glu Asp Asp Arg Val Lys
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 Arg Tyr Leu Glu Gly Thr Ser Cys Ile Ala Gly Val Leu Val Pro Ala
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 Lys Asp Gln Pro Gly Arg Gln Glu Lys Met Ser Ile Tyr Gln Ala Met
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 Trp Lys Gly Val Leu Arg Pro Gly Thr Ala Leu Val Leu Leu Glu Ala
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 Gln Ala Ala Thr Gly Phe Val Ile Asp Pro Val Arg Asn Leu Arg Leu
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 Tyr Thr Gly Gln Gln Ile Ser Leu Phe Gln Ala Met Gln Lys Asp Leu
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Gln Glu Gln Thr Leu Arg Asp Ala Thr Met Glu Val Gln Arg Gly Gln					
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Phe Gln Gly Arg Pro Val Ser Val Trp Asp Val Leu Phe Ser Ser Tyr					
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Glu Thr Glu Glu Arg Leu Ser Lys Val Ser Phe Arg Gly Leu Arg Arg					
	2675		2680		2685
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Cys Val Pro Asp Pro Asp Thr Gly Leu Tyr Met Leu Gln Leu Ala Gly					
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Tyr Cys Cys Asp Phe Ser Ser Thr Ala Ile Glu Leu Val Gln Thr Asn
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<210> 56

<211> 509

<212> PRT

<213> Homo sapiens

<400> 56

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Arg Lys Ser Val Val His Cys Ser Lys Ile Trp Ser Cys Arg Lys Arg

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 <212> DNA
 <213> Homo sapiens

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 <213> Homo sapiens

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 Gly Pro Glu Glu Asp Thr Ala Tyr Leu Asp Gly Val Ser Leu Pro Asp
 65 70 75 80
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 Met Gln Leu Leu Gln Glu Ser Leu Ala Gln Ala Arg Leu Gly Ser Arg
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<210> 59

<211> 2012

<212> DNA

<213> Homo sapiens

<400> 59

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 <211> 495
 <212> PRT
 <213> Homo sapiens

<400> 60

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Pro Thr Asp Glu Gln Phe Ala Ala Ile Ile Val Leu Gly Phe Ala Thr					
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<211> 2384

<212> DNA

<213> Homo sapiens

<400> 61

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Cys	Ile	Ala	Tyr	Ser	Gln	Leu	Arg	Asp	Gln	Cys	Ile	Val	Asp	Asp	Ile
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Tyr	Cys	Tyr	Gly	Arg	Gly	Ile	Gly	Glu	Trp	His	Cys	Gln	Pro	Leu	Gln
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Ser	Gly	Phe	Arg	Val	Glu	Tyr	Glu	Leu	Ser	Glu	Glu	Gly	Asp	Glu	Pro
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Gln	Tyr	Leu	Asp	Leu	Pro	Ser	Thr	Ala	Thr	Ser	Val	Asn	Ile	Pro	Asp
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1875	1880	1885
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Gln Leu Val Thr Leu	Pro His Pro Asn Leu His	Gly Pro Glu Ile Leu
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Asp Val Pro Ser Thr	Val Gln Lys Thr Pro Phe	Val Thr His Pro Gly
1985	1990	1995
Tyr Asp Thr Gly Asn	Gly Ile Gln Leu Pro Gly	Thr Ser Gly Gln Gln
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Asp Glu Trp Glu Arg	Met Ser Glu Ser Gly Phe	Lys Leu Leu Cys Gln
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Cys Leu Gly Phe Gly	Ser Gly His Phe Arg Cys	Asp Ser Ser Arg Trp
2180	2185	2190
Cys His Asp Asn Gly	Val Asn Tyr Lys Ile Gly	Glu Lys Trp Asp Arg
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 2275 2280 2285
 Gly Gln Ser Tyr Asn Gln Tyr Ser Gln Arg Tyr His Gln Arg Thr Asn
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<210> 68

<211> 3252

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 779

<223> n = A,T,C or G

<400> 68

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<210> 69

<211> 756

<212> PRT

<213> Homo sapiens

<400> 69

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Ser	Gln	Asn	Lys	Asp	Lys	Thr	Leu	Glu	Lys	His	Leu	Lys	Thr	Val	Glu
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Lys	Val	Leu	Phe	Tyr	Arg	Trp	Leu	Val	Ala	Met	Phe	Asp	Phe	Ile	Asp
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Arg	Lys	Glu	Gln	Ile	Asn	Leu	Leu	Tyr	Gly	Phe	Phe	Phe	Ala	Ser	Leu
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Gly	Ser	Phe	Pro	Leu	Glu	Gln	Leu	Gln	Ser	Phe	Pro	Gln	Leu	Leu	Gln
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Asn	Ile	His	Cys	Leu	Glu	Leu	Pro	Ser	Gln	Met	Gly	Ser	Val	Leu	Asn
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Ile	Trp	Tyr	Lys	Val	Asn	Asn	Tyr	Glu	His	Gly	Lys	Glu	Phe	Thr	Asn
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Phe	Leu	Asp	Thr	Ile	Ile	Arg	Ala	Glu	Cys	Phe	Leu	Gln	Glu	Gly	Tyr
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Tyr	Ser	Cys	Glu	Ala	Phe	Leu	Tyr	Lys	Ser	Leu	Pro	Leu	Trp	Asp	Gly
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Val	Ala	Glu	Tyr	Lys	Asn	Ser	Leu	Asn	Val	Val	His	His	Pro	Ser	Phe
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Leu	Ser	Tyr	Ala	Val	Ser	Phe	Leu	Leu	Gln	Glu	Ser	Pro	Glu	Glu	Arg
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Asp	Tyr	Leu	Phe	Ser	Gln	Gly	Leu	Gln	Gly	Leu	Lys	Leu	Phe	Ile	Arg
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Ser	Ser	Val	His	His	Ser	Ser	Ile	Pro	Arg	Ala	Glu	Gly	Ile	Asn	Cys
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<210> 70

<211> 1559

<212> DNA

<213> Homo sapiens

<400> 70

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<210> 71

<211> 338

<212> PRT

<213> Homo sapiens

<400> 71

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Gly Val Asn Asp Ser Phe Pro Asp Gly Asp Tyr Asp Ala Asn Leu Glu
          35          40          45
Ala Ala Ala Pro Cys His Ser Cys Asn Leu Leu Asp Asp Ser Ala Leu
          50          55          60
Pro Phe Phe Ile Leu Thr Ser Val Leu Gly Ile Leu Ala Ser Ser Thr
          65          70          75          80
Val Leu Phe Met Leu Phe Arg Pro Leu Phe Arg Trp Gln Leu Cys Pro
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Ile Val Val Pro Val Leu Ala Pro Gly Leu Gly Ser Thr Arg Ser Ser
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          145          150          155          160
Ala Gly Gln Val Pro Gly Leu Thr Leu Gly Leu Thr Val Gly Ile Trp
          165          170          175
Gly Val Ala Ala Leu Leu Thr Leu Pro Val Thr Leu Ala Ser Gly Ala
          180          185          190
Ser Gly Gly Leu Cys Thr Leu Ile Tyr Ser Thr Glu Leu Lys Ala Leu
          195          200          205
Gln Ala Thr His Thr Val Ala Cys Leu Ala Ile Phe Val Leu Leu Pro
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Leu Gly Leu Phe Gly Ala Lys Gly Leu Lys Lys Ala Leu Gly Met Gly
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 290 295 300
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<210> 72
 <211> 817
 <212> DNA
 <213> Homo sapiens

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<210> 73
 <211> 130
 <212> PRT
 <213> Homo sapiens

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 35 40 45
 Gly Gly Leu Ala Val Ala Gly Leu Pro Ala Leu Gly Phe Thr Gly Ala
 50 55 60
 Gly Ile Ala Ala Asn Ser Val Ala Ala Ser Leu Met Ser Trp Ser Ala
 65 70 75 80
 Ile Leu Asn Gly Gly Gly Val Pro Ala Gly Gly Leu Val Ala Thr Leu
 85 90 95
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<210> 74
<211> 2861
<212> DNA
<213> Homo sapiens

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 <211> 187
 <212> PRT
 <213> Homo sapiens

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 35 40 45
 Arg Glu Ile Val Ala Leu Lys Thr Lys Leu Lys Glu Cys Glu Ala Ser
 50 55 60
 Lys Asp Gln Asn Thr Pro Val Val His Pro Pro Thr Pro Gly Ser
 65 70 75 80
 Cys Gly His Gly Gly Val Val Asn Ile Ser Lys Pro Ser Val Val Gln
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 Leu Asn Trp Arg Gly Phe Ser Tyr Leu Tyr Gly Ala Trp Gly Arg Asp
 100 105 110
 Tyr Ser Pro Gln His Pro Asn Lys Gly Leu Tyr Trp Val Ala Pro Leu
 115 120 125
 Asn Thr Asp Gly Arg Leu Leu Glu Tyr Tyr Ile Leu Tyr Asn Thr Leu
 130 135 140
 Asp Asp Leu Leu Leu Tyr Ile Asn Ala Arg Glu Leu Arg Ile Thr Tyr
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 <211> 266
 <212> PRT
 <213> Homo sapiens

<400> 77

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 50 55 60
 Gly Gln Val Gly Gly Glu Ile Asn Val Glu Met Asp Ala Ala Pro Gly
 65 70 75 80
 Val Asp Leu Ser Arg Ile Leu Asn Glu Met Arg Asp Gln Tyr Glu Lys
 85 90 95
 Met Ala Glu Lys Asn Arg Lys Asp Ala Glu Asp Trp Phe Phe Ser Lys
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 145 150 155 160
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 165 170 175
 Gln Gly Leu Ile Gly Ser Val Glu Glu Gln Leu Ala Gln Leu Arg Cys
 180 185 190
 Glu Met Glu Gln Gln Asn Gln Glu Tyr Lys Ile Leu Leu Asp Val Lys
 195 200 205
 Thr Arg Leu Glu Gln Glu Ile Ala Thr Tyr Arg Arg Leu Leu Glu Gly
 210 215 220
 Glu Asp Ala His Leu Thr Gln Tyr Lys Lys Glu Pro Val Thr Thr Arg
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<210> 78

<211> 1689

<212> DNA

<213> Homo sapiens

<400> 78

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<210> 79
 <211> 373
 <212> PRT
 <213> Homo sapiens

<400> 79

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Ala	Lys	Gly	Asp	Asn	Val	Tyr	Glu	Phe	His	Leu	Glu	Phe	Leu	Asp	Leu
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Glu	Ser	Asp	Ala	Glu	Met	Glu	Leu	Arg	Ala	Lys	Glu	Glu	Glu	Arg	Leu
		115				120					125				
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225				230					235					240	
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Gly	Cys	Leu	Val	Glu	Ala	Val	Ser	Val	Ile	Gln	Ser	Ile	Pro	Ile	Phe
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Asn Glu Thr Gly Arg Phe Ser Phe Thr Leu Pro Tyr Pro Val Lys Ile
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 Lys Val Arg Phe Ser Phe Phe Leu Gln Ile Tyr Leu Ile Met Ile Phe
 325 330 335
 Leu Gly Leu Tyr Ile Asn Phe Arg His Leu Tyr Lys Gln Arg Arg Arg
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 Arg Tyr Gly Lys Lys Arg Lys Arg Ser Thr Lys Lys Lys Asp Leu Asp
 355 360 365
 Gly Phe Leu Pro Val
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 <211> 1824
 <212> DNA
 <213> Homo sapiens

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 <211> 142
 <212> PRT
 <213> Homo sapiens

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Thr	Thr	Gly	Asp	Ala	Met	Ser	Lys	Arg	Ser	Lys	Phe	Ala	Leu	Ile	Thr
65					70					75					
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Val	Ile	Ser	Asp	Arg	Lys	Glu	Leu	Glu	Glu	Asp	Phe	Ile	Lys	Ser	Glu
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<211> 10174

<212> DNA

<213> Homo sapiens

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<211> 2701

<212> PRT

<213> Homo sapiens

<400> 83

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Gly Ile Ser Arg Arg Met Pro Pro Pro Ala Asn Leu Pro Ser Leu Lys
50      55      60
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65      70      75      80
Gly Thr Gly Trp Ala Ser Lys Gln Glu Gln His Glu Glu Glu Lys Thr
85      90      95
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Glu Thr Asn Lys Gly Leu Arg Gly Arg Gly Pro Pro Pro Ser Trp Ala
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 Arg Pro Ser Thr Leu Arg Arg Pro Ala Tyr Arg Asp Asn Gln Trp Asn
 1365 1370 1375
 Pro Arg Gln Ser Glu Val Pro Lys Pro Glu Asp Gly Glu Pro Pro Arg
 1380 1385 1390
 Arg His Glu Gln Phe Ile Pro Ile Ala Ala Asp Lys Arg Pro Pro Lys
 1395 1400 1405
 Phe Glu Arg Lys Phe Asp Pro Ala Arg Glu Arg Pro Arg Arg Gln Arg
 1410 1415 1420
 Pro Thr Arg Pro Pro Arg Gln Asp Lys Pro Pro Arg Phe Arg Arg Leu
 1425 1430 1435 1440
 Arg Glu Arg Glu Ala Ala Ser Lys Ser Asn Glu Val Val Ala Val Pro
 1445 1450 1455
 Thr Asn Gly Thr Val Asn Asn Val Ala Gln Glu Pro Val Asn Thr Leu
 1460 1465 1470
 Gly Asp Ile Ser Gly Asn Lys Thr Pro Asp Leu Ser Asn Gln Asn Ser
 1475 1480 1485
 Ser Asp Gln Ala Asn Glu Glu Trp Glu Thr Ala Ser Glu Ser Ser Asp
 1490 1495 1500
 Phe Asn Glu Arg Arg Glu Arg Asp Glu Lys Lys Asn Ala Asp Leu Asn
 1505 1510 1515 1520
 Ala Gln Thr Val Val Lys Val Gly Glu Asn Val Leu Pro Pro Lys Arg
 1525 1530 1535
 Glu Ile Ala Lys Arg Ser Phe Ser Ser Gln Arg Pro Val Asp Arg Gln
 1540 1545 1550
 Asn Arg Arg Gly Asn Asn Gly Pro Pro Lys Ser Gly Arg Asn Phe Ser
 1555 1560 1565
 Gly Pro Arg Asn Glu Arg Arg Ser Gly Pro Pro Ser Lys Ser Gly Lys
 1570 1575 1580
 Arg Gly Pro Phe Asp Asp Gln Pro Ala Gly Thr Thr Gly Val Asp Leu
 1585 1590 1595 1600
 Ile Asn Gly Ser Ser Ala His His Gln Glu Gly Val Pro Asn Gly Thr
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 Gly Gln Lys Asn Ser Lys Asp Ser Thr Gly Lys Lys Arg Glu Asp Pro
 1620 1625 1630
 Lys Pro Gly Pro Lys Lys Pro Lys Glu Lys Val Asp Ala Leu Ser Gln
 1635 1640 1645
 Phe Asp Leu Asn Asn Tyr Ala Ser Val Val Ile Ile Asp Asp His Pro
 1650 1655 1660
 Glu Val Thr Val Ile Glu Asp Pro Gln Ser Asn Leu Asn Asp Asp Gly
 1665 1670 1675 1680
 Phe Thr Glu Val Val Ser Lys Lys Gln Gln Lys Arg Leu Gln Asp Glu
 1685 1690 1695
 Glu Arg Arg Lys Lys Glu Glu Gln Val Ile Gln Val Trp Asn Lys Lys

1700	1705	1710
Asn Ala Asn Glu Lys Gly Arg Ser Gln Thr Ser Lys Leu Pro Pro Arg		
1715	1720	1725
Phe Ala Lys Lys Gln Ala Thr Gly Ile Gln Gln Ala Gln Ser Ser Ala		
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Ser Val Pro Pro Leu Ala Ser Ala Pro Leu Pro Pro Ser Thr Ser Ala		
1745	1750	1755
Ser Val Pro Ala Ser Thr Ser Ala Pro Leu Pro Ala Thr Leu Thr Pro		1760
1765	1770	1775
Val Pro Ala Ser Thr Ser Ala Pro Val Pro Ala Ser Thr Leu Ala Pro		
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Val Leu Ala Ser Thr Ser Ala Pro Val Pro Ala Ser Pro Leu Ala Pro		
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Val Ser Ala Ser Ala Ser Val Ser Ala Ser Val Pro Ala Ser Thr Ser		
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Ala Ala Ala Ile Thr Ser Ser Ala Pro Ala Ser Ala Pro Ala Pro		
1825	1830	1835
Thr Pro Ile Leu Ala Ser Val Ser Thr Pro Ala Ser Val Thr Ile Leu		
1845	1850	1855
Ala Ser Ala Ser Ile Pro Ile Leu Ala Ser Ala Leu Ala Ser Thr Ser		
1860	1865	1870
Ala Pro Thr Pro Ala Pro Ala Ala Ser Ser Pro Ala Ala Pro Val Ile		
1875	1880	1885
Thr Ala Pro Thr Ile Pro Ala Ser Ala Pro Thr Ala Ser Val Pro Leu		
1890	1895	1900
Ala Pro Ala Ser Ala Ser Ala Pro Ala Pro Ala Pro Thr Pro Val Ser		
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Ala Pro Asn Pro Ala Pro Pro Ala Pro Ala Gln Thr Gln Ala Gln Thr		
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His Lys Pro Val Gln Asn Pro Leu Gln Thr Thr Ser Gln Ser Ser Lys		
1940	1945	1950
Gln Pro Pro Pro Ser Ile Arg Leu Pro Ser Ala Gln Thr Pro Asn Gly		
1955	1960	1965
Thr Asp Tyr Val Ala Ser Gly Lys Ser Ile Gln Thr Pro Gln Ser His		
1970	1975	1980
Gly Thr Leu Thr Ala Glu Leu Trp Asp Asn Lys Val Ala Pro Pro Ala		
1985	1990	1995
Val Leu Asn Asp Ile Ser Lys Lys Leu Gly Pro Ile Ser Pro Pro Gln		
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Pro Pro Ser Val Ser Ala Trp Asn Lys Pro Leu Thr Ser Phe Gly Ser		
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Ala Pro Ser Ser Glu Gly Ala Lys Asn Gly Gln Glu Ser Gly Leu Glu		
2035	2040	2045
Ile Gly Thr Asp Thr Ile Gln Phe Gly Ala Pro Ala Ser Asn Gly Asn		
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Glu Asn Glu Val Val Pro Val Leu Ser Glu Lys Ser Ala Asp Lys Ile		
2065	2070	2075
Pro Glu Pro Lys Glu Gln Arg Gln Lys Gln Pro Arg Ala Gly Pro Ile		
2085	2090	2095
Lys Ala Gln Lys Leu Pro Asp Leu Ser Pro Val Glu Asn Lys Glu His		
2100	2105	2110
Lys Pro Gly Pro Ile Gly Lys Glu Arg Ser Leu Lys Asn Arg Lys Val		
2115	2120	2125
Lys Asp Ala Gln Gln Val Glu Pro Glu Gly Gln Glu Lys Pro Ser Pro		
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Ala Thr Val Arg Ser Thr Asp Pro Val Thr Thr Lys Glu Thr Lys Ala		
2145	2150	2155
Val Ser Glu Met Ser Thr Glu Ile Gly Thr Met Ile Ser Val Ser Ser		
2165	2170	2175

Ala	Glu	Tyr	Gly	Thr	Asn	Ala	Lys	Glu	Ser	Val	Thr	Asp	Tyr	Thr	Thr	2180	2185	2190
Pro	Ser	Ser	Ser	Leu	Pro	Asn	Thr	Val	Ala	Thr	Asn	Asn	Thr	Lys	Met	2195	2200	2205
Glu	Asp	Thr	Leu	Val	Asn	Asn	Val	Pro	Leu	Pro	Asn	Thr	Leu	Pro	Leu	2210	2215	2220
Pro	Lys	Arg	Glu	Thr	Ile	Gln	Gln	Ser	Ser	Ser	Leu	Thr	Ser	Val	Pro	2225	2230	2235
Pro	Thr	Thr	Phe	Ser	Leu	Thr	Phe	Lys	Met	Glu	Ser	Ala	Arg	Lys	Ala	2245	2250	2255
Trp	Glu	Asn	Ser	Pro	Asn	Val	Arg	Glu	Lys	Gly	Ser	Pro	Val	Thr	Ser	2260	2265	2270
Thr	Ala	Pro	Pro	Ile	Ala	Thr	Gly	Val	Ser	Ser	Ser	Ala	Ser	Gly	Pro	2275	2280	2285
Ser	Thr	Ala	Asn	Tyr	Asn	Ser	Phe	Ser	Ser	Ala	Ser	Met	Pro	Gln	Ile	2290	2295	2300
Pro	Val	Ala	Ser	Val	Thr	Pro	Thr	Ala	Ser	Leu	Ser	Gly	Ala	Gly	Thr	2305	2310	2315
Tyr	Thr	Thr	Ser	Ser	Leu	Ser	Thr	Lys	Ser	Thr	Thr	Thr	Ser	Asp	Pro	2325	2330	2335
Pro	Asn	Ile	Cys	Lys	Val	Lys	Pro	Gln	Gln	Leu	Gln	Thr	Ser	Ser	Leu	2340	2345	2350
Pro	Ser	Ala	Ser	His	Phe	Ser	Gln	Leu	Ser	Cys	Met	Pro	Ser	Leu	Ile	2355	2360	2365
Ala	Gln	Gln	Gln	Gln	Asn	Pro	Gln	Val	Tyr	Val	Ser	Gln	Ser	Ala	Ala	2370	2375	2380
Ala	Gln	Ile	Pro	Ala	Phe	Tyr	Met	Asp	Thr	Ser	His	Leu	Phe	Asn	Thr	2385	2390	2395
Gln	His	Ala	Arg	Leu	Ala	Pro	Pro	Ser	Leu	Ala	Gln	Gln	Gln	Gly	Phe	2405	2410	2415
Gln	Pro	Gly	Leu	Ser	Gln	Pro	Thr	Ser	Val	Gln	Gln	Ile	Pro	Ile	Pro	2420	2425	2430
Ile	Tyr	Ala	Pro	Leu	Gln	Gly	Gln	His	Gln	Ala	Gln	Leu	Ser	Leu	Gly	2435	2440	2445
Ala	Gly	Pro	Ala	Val	Ser	Gln	Ala	Gln	Glu	Leu	Phe	Ser	Ser	Ser	Leu	2450	2455	2460
Gln	Pro	Tyr	Arg	Ser	Gln	Pro	Ala	Phe	Met	Gln	Ser	Ser	Leu	Ser	Gln	2465	2470	2475
Pro	Ser	Val	Val	Leu	Ser	Gly	Thr	Ala	Ile	His	Asn	Phe	Pro	Thr	Val	2485	2490	2495
Gln	His	Gln	Glu	Leu	Ala	Lys	Ala	Gln	Ser	Gly	Leu	Ala	Phe	Gln	Gln	2500	2505	2510
Thr	Ser	Asn	Thr	Gln	Pro	Ile	Pro	Ile	Leu	Tyr	Glu	His	Gln	Leu	Gly	2515	2520	2525
Gln	Ala	Ser	Gly	Leu	Gly	Gly	Ser	Gln	Leu	Ile	Asp	Thr	His	Leu	Leu	2530	2535	2540
Gln	Ala	Arg	Ala	Asn	Leu	Thr	Gln	Ala	Ser	Asn	Leu	Tyr	Ser	Gly	Gln	2545	2550	2555
Val	Gln	Gln	Pro	Gly	Gln	Thr	Asn	Phe	Tyr	Asn	Thr	Ala	Gln	Ser	Pro	2565	2570	2575
Ser	Ala	Leu	Gln	Gln	Val	Thr	Val	Pro	Leu	Pro	Ala	Ser	Gln	Leu	Ser	2580	2585	2590
Leu	Pro	Asn	Phe	Gly	Ser	Thr	Gly	Gln	Pro	Leu	Ile	Ala	Leu	Pro	Gln	2595	2600	2605
Thr	Leu	Gln	Pro	Pro	Leu	Gln	His	Thr	Thr	Pro	Gln	Ala	Gln	Ala	Gln	2610	2615	2620
Ser	Leu	Ser	Arg	Pro	Ala	Gln	Val	Ser	Gln	Pro	Phe	Arg	Gly	Leu	Ile	2625	2630	2635
Pro	Ala	Gly	Thr	Gln	His	Ser	Met	Ile	Ala	Thr	Thr	Gly	Lys	Met	Ser	2640		

	2645		2650		2655
Glu Met Glu Leu Lys Ala Phe Gly Ser Gly Ile Asp Ile Lys Pro Gly					
	2660		2665		2670
Thr Pro Pro Ile Ala Gly Arg Ser Thr Thr Pro Thr Ser Ser Pro Ser					
	2675		2680		2685
Gly Leu Leu Leu Gln Val Arg Thr Ala Ser Pro Ala Lys					
	2690		2695		2700

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 <211> 597
 <212> DNA
 <213> Homo sapiens

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 ggctctgccg tagttttgcc cctggccagg attgctacag ttgtgattgg aggagttgtg 180
 gccatggcgg ctgtgcccac ggtgctcagt gccatgggct tcactgcggc gggaaatgcc 240
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 gcctcgggca gccttgtggg tactctgcag tcaactggag caactggact ctccggattg 360
 accaagttca tcctgggctc cattgggtct gccattgcgg ctgtcattgc gaggttctac 420
 tagctccctg cccctcgccc tgcagagaag agaaccatgc caggggagaa ggcacccagc 480
 catcctgacc cagcgaggag ccaactatcc caaatatacc tgggtgaaat ataccaaatt 540
 ctgcatctcc agaggaaaat aagaaataaa gatgaattgt tgcaactctt aaaaaaa 597

<210> 85
 <211> 122
 <212> PRT
 <213> Homo sapiens

<400> 85
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 1 5 10 15
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 Ile Ala Thr Val Val Ile Gly Gly Val Val Ala Met Ala Ala Val Pro
 35 40 45
 Met Val Leu Ser Ala Met Gly Phe Thr Ala Ala Gly Ile Ala Ser Ser
 50 55 60
 Ser Ile Ala Ala Lys Met Met Ser Ala Ala Ala Ile Ala Asn Gly Gly
 65 70 75 80
 Gly Val Ala Ser Gly Ser Leu Val Gly Thr Leu Gln Ser Leu Gly Ala
 85 90 95
 Thr Gly Leu Ser Gly Leu Thr Lys Phe Ile Leu Gly Ser Ile Gly Ser
 100 105 110
 Ala Ile Ala Ala Val Ile Ala Arg Phe Tyr
 115 120

<210> 86
 <211> 1032
 <212> DNA
 <213> Homo sapiens

<400> 86
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 gctggacgtc cccacggcgg cgggtgcaggc gtccctctg caagcgtagt acttctttgg 180

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<210> 87

<211> 303

<212> PRT

<213> Homo sapiens

<400> 87

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20          25          30
Ala Ala Val Gln Ala Ser Pro Leu Gln Ala Leu Asp Phe Phe Gly Asn
35          40          45
Gly Pro Pro Val Asn Tyr Lys Thr Gly Asn Leu Tyr Leu Arg Gly Pro
50          55          60
Leu Lys Lys Ser Asn Ala Pro Leu Val Asn Val Thr Leu Tyr Tyr Glu
65          70          75          80
Ala Leu Cys Gly Gly Cys Arg Ala Phe Leu Ile Arg Glu Leu Phe Pro
85          90          95
Thr Trp Leu Leu Val Met Glu Ile Leu Asn Val Thr Ser Val Pro Tyr
100         105         110
Gly Asn Ala Gln Glu Gln Asn Val Ser Gly Arg Trp Glu Phe Lys Cys
115         120         125
Gln Leu Gly Glu Glu Glu Cys Lys Phe Asn Lys Val Glu Ala Cys Val
130         135         140
Leu Asp Glu Leu Asp Met Glu Leu Ala Phe Leu Thr Met Ser Gly Met
145         150         155         160
Ala Trp Lys Ser Leu Arg Thr Trp Arg Glu Val Cys His Tyr Ala Cys
165         170         175
Ser Ser Thr Pro Gln Gly Cys Arg Gln Asn Tyr His Gly Val Cys Asn
180         185         190
Gly Gly Pro Arg His Ala Ala His Ala Arg Gln Arg Pro Ala Asp Arg
195         200         205
Cys Ser Pro Ala Thr Ala Arg Val Cys Ala Leu Gly His Arg Gln Trp
210         215         220
Glu Thr Leu Gly Arg Ser Asp Pro Ala Pro Tyr Pro Cys Leu Pro Val
225         230         235         240
Val Pro Gly Gln Glu Ala Gly Cys Leu Pro Phe Leu Asn Gln Leu Pro
245         250         255
Pro Glu Cys Leu Leu Arg Val Leu Ala Gly Gly Leu Arg Arg Ala His
260         265         270
Gly Arg Arg Val Gly Thr Arg Leu Pro Ala Phe Phe Ser Asp Pro Asp
275         280         285
Pro Arg His Leu Leu Leu Thr Asn Trp Lys Ile Leu Cys Ile Pro

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290

295

300

<210> 88
 <211> 905
 <212> DNA
 <213> Homo sapiens

<400> 88
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 taatttgatc ctcaggaatt tgttctgccc tcattctggcc ctggccagct ctgcatttga 180
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 aacacctgct gcctgggctt catagcattc gcctactccg tgaagtctag ggacaggaa 540
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<210> 89
 <211> 132
 <212> PRT
 <213> Homo sapiens

<400> 89
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 20 25 30
 Gly Pro His Asn Pro Ala Pro Pro Thr Ser Thr Val Ile His Ile Arg
 35 40 45
 Ser Glu Thr Ser Val Pro Asp His Val Val Trp Ser Leu Phe Asn Thr
 50 55 60
 Leu Phe Met Asn Thr Cys Leu Gly Phe Ile Ala Phe Ala Tyr Ser
 65 70 75 80
 Val Lys Ser Arg Asp Arg Lys Met Val Gly Asp Val Thr Gly Ala Gln
 85 90 95
 Ala Tyr Ala Ser Thr Ala Lys Cys Leu Asn Ile Trp Ala Leu Ile Leu
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 Gly Ile Phe Met Thr Ile Leu Leu Val Ile Ile Pro Val Leu Val Val
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 Gln Ala Gln Arg
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<210> 90
 <211> 2499
 <212> DNA
 <213> Homo sapiens

<400> 90
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<210> 91

<211> 291

<212> PRT

<213> Homo sapiens

<400> 91

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20           25           30
Gly Leu Gly Pro Val Val Arg Cys Glu Pro Cys Asp Ala Arg Ala Leu
35           40           45
Ala Gln Cys Ala Pro Pro Pro Ala Val Cys Ala Glu Leu Val Arg Glu
50           55           60
Pro Gly Cys Gly Cys Cys Leu Thr Cys Ala Leu Ser Glu Gly Gln Pro
65           70           75           80
Cys Gly Ile Tyr Thr Glu Arg Cys Gly Ser Gly Leu Arg Cys Gln Pro

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				85						90					95				
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Leu	Cys	Val	Asn	Ala	Ser	Ala	Val	Ser	Arg	Leu	Arg	Ala	Tyr	Leu	Leu				
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Pro	Ala	Pro	Pro	Ala	Pro	Gly	Asn	Ala	Ser	Glu	Ser	Glu	Glu	Asp	Arg				
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Ser	Ala	Gly	Ser	Val	Glu	Ser	Pro	Ser	Val	Ser	Ser	Thr	His	Arg	Val				
145					150					155					160				
Ser	Asp	Pro	Lys	Phe	His	Pro	Leu	His	Ser	Lys	Ile	Ile	Ile	Ile	Lys				
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Lys	Gly	His	Ala	Lys	Asp	Ser	Gln	Arg	Tyr	Lys	Val	Asp	Tyr	Glu	Ser				
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Gln	Ser	Thr	Asp	Thr	Gln	Asn	Phe	Ser	Ser	Glu	Ser	Lys	Arg	Glu	Thr				
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Glu	Tyr	Gly	Pro	Cys	Arg	Arg	Glu	Met	Glu	Asp	Thr	Leu	Asn	His	Leu				
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Lys	Phe	Leu	Asn	Val	Leu	Ser	Pro	Arg	Gly	Val	His	Ile	Pro	Asn	Cys				
225					230					235					240				
Asp	Lys	Lys	Gly	Phe	Tyr	Lys	Lys	Lys	Gln	Cys	Arg	Pro	Ser	Lys	Gly				
			245						250					255					
Arg	Lys	Arg	Gly	Phe	Cys	Trp	Cys	Val	Asp	Lys	Tyr	Gly	Gln	Pro	Leu				
		260					265					270							
Pro	Gly	Tyr	Thr	Thr	Lys	Gly	Lys	Glu	Asp	Val	His	Cys	Tyr	Ser	Met				
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Gln	Ser	Lys																	
	290																		

<210> 92
 <211> 1639
 <212> DNA
 <213> Homo sapiens

<400> 92
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 gaaacttcaa gcaaatctac ttcaacactt catgtattgt gtgggtctgt tgtagggttg 480
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 acaattgggt acccagttaa attttcattt cagataaaca acaataattt ttttagtata 1260
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 aactattaaa acagccaaaa ctccacagtc aatattagta atttcttgct ggttgaaact 1440

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<210> 93

<211> 99

<212> PRT

<213> Homo sapiens

<400> 93

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 20          25          30
Arg Cys Gln Cys Ile Lys Thr Tyr Ser Lys Pro Phe His Pro Lys Phe
 35          40          45
Ile Lys Glu Leu Arg Val Ile Glu Ser Gly Pro His Cys Ala Asn Thr
 50          55          60
Glu Ile Ile Val Lys Leu Ser Asp Gly Arg Glu Leu Cys Leu Asp Pro
 65          70          75          80
Lys Glu Asn Trp Val Gln Arg Val Val Glu Lys Phe Leu Lys Arg Ala
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Glu Asn Ser

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<210> 94

<211> 1840

<212> DNA

<213> Homo sapiens

<400> 94

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<210> 95

<211> 426

<212> PRT

<213> Homo sapiens

<400> 95

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 20      25      30
Pro Asp Cys Pro Ser Cys Ala Leu Ala Ala Leu Pro Lys Asp Val Pro
 35      40      45
Asn Ser Gln Pro Glu Met Val Glu Ala Val Lys Lys His Ile Leu Asn
 50      55      60
Met Leu His Leu Lys Lys Arg Pro Asp Val Thr Gln Pro Val Pro Lys
 65      70      75      80
Ala Ala Leu Leu Asn Ala Ile Arg Lys Leu His Val Gly Lys Val Gly
 85      90      95
Glu Asn Gly Tyr Val Glu Ile Glu Asp Asp Ile Gly Arg Arg Ala Glu
100      105      110
Met Asn Glu Leu Met Glu Gln Thr Ser Glu Ile Ile Thr Phe Ala Glu
115      120      125
Ser Gly Thr Ala Arg Lys Thr Leu His Phe Glu Ile Ser Lys Glu Gly
130      135      140
Ser Asp Leu Ser Val Val Glu Arg Ala Glu Val Trp Leu Phe Leu Lys
145      150      155      160
Val Pro Lys Ala Asn Arg Thr Arg Thr Lys Val Thr Ile Arg Leu Phe
165      170      175
Gln Gln Gln Lys His Pro Gln Gly Ser Leu Asp Thr Gly Glu Glu Ala
180      185      190
Glu Glu Val Gly Leu Lys Gly Glu Arg Ser Glu Leu Leu Leu Ser Glu
195      200      205
Lys Val Val Asp Ala Arg Lys Ser Thr Trp His Val Phe Pro Val Ser
210      215      220
Ser Ser Ile Gln Arg Leu Leu Asp Gln Gly Lys Ser Ser Leu Asp Val
225      230      235      240
Arg Ile Ala Cys Glu Gln Cys Gln Glu Ser Gly Ala Ser Leu Val Leu
245      250      255
Leu Gly Lys Lys Lys Lys Lys Glu Glu Gly Glu Gly Lys Lys Lys
260      265      270
Gly Gly Gly Glu Gly Gly Ala Gly Ala Asp Glu Glu Lys Glu Gln Ser
275      280      285
His Arg Pro Phe Leu Met Leu Gln Ala Arg Gln Ser Glu Asp His Pro
290      295      300
His Arg Arg Arg Arg Arg Gly Leu Glu Cys Asp Gly Lys Val Asn Ile
305      310      315      320
Cys Cys Lys Lys Gln Phe Phe Val Ser Phe Lys Asp Ile Gly Trp Asn
325      330      335
Asp Trp Ile Ile Ala Pro Ser Gly Tyr His Ala Asn Tyr Cys Glu Gly
340      345      350
Glu Cys Pro Ser His Ile Ala Gly Thr Ser Gly Ser Ser Leu Ser Phe
355      360      365
His Ser Thr Val Ile Asn His Tyr Arg Met Arg Gly His Ser Pro Phe

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370	375	380
Ala Asn Leu Lys Ser Cys Cys Val Pro Thr Lys	Leu Arg Pro Met Ser	
385	390	395
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Asn Met Ile Val Glu Glu Cys Gly Cys Ser		415
	420	425

<210> 96
 <211> 4637
 <212> DNA
 <213> Homo sapiens

<400> 96
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<210> 97

<211> 1051

<212> PRT

<213> Homo sapiens

<400> 97

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Phe Asn Leu Asp Thr Arg Phe Leu Val Val Lys Glu Ala Gly Asn Pro
35          40          45
Gly Ser Leu Phe Gly Tyr Ser Val Ala Leu His Arg Gln Thr Glu Arg
50          55          60
Gln Gln Arg Tyr Leu Leu Leu Ala Gly Ala Pro Arg Glu Leu Ala Val
65          70          75          80
Pro Asp Gly Tyr Thr Asn Arg Thr Gly Ala Val Tyr Leu Cys Pro Leu
85          90          95
Thr Ala His Lys Asp Asp Cys Glu Arg Met Asn Ile Thr Val Lys Asn
100         105         110
Asp Pro Gly His His Ile Ile Glu Asp Met Trp Leu Gly Val Thr Val
115         120         125
Ala Ser Gln Gly Pro Ala Gly Arg Val Leu Val Cys Ala His Arg Tyr
130         135         140

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				165					170						175
Trp	Gln	Thr	Tyr	His	Asn	Glu	Met	Cys	Asn	Ser	Asn	Thr	Asp	Tyr	Leu
			180					185					190		
Glu	Thr	Gly	Met	Cys	Gln	Leu	Gly	Thr	Ser	Gly	Gly	Phe	Thr	Gln	Asn
		195					200					205			
Thr	Val	Tyr	Phe	Gly	Ala	Pro	Gly	Ala	Tyr	Asn	Trp	Lys	Gly	Asn	Ser
	210					215					220				
Tyr	Met	Ile	Gln	Arg	Lys	Glu	Trp	Asp	Leu	Ser	Glu	Tyr	Ser	Tyr	Lys
225					230					235					240
Asp	Pro	Glu	Asp	Gln	Gly	Asn	Leu	Tyr	Ile	Gly	Tyr	Thr	Met	Gln	Val
				245					250						255
Gly	Ser	Phe	Ile	Leu	His	Pro	Lys	Asn	Ile	Thr	Ile	Val	Thr	Gly	Ala
			260					265					270		
Pro	Arg	His	Arg	His	Met	Gly	Ala	Val	Phe	Leu	Leu	Ser	Gln	Glu	Ala
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Ala	Tyr	Phe	Gly	Ser	Ala	Ile	Ala	Leu	Ala	Asp	Leu	Asn	Asn	Asp	Gly
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Trp	Gln	Asp	Leu	Leu	Val	Gly	Ala	Pro	Tyr	Tyr	Phe	Glu	Arg	Lys	Glu
			325						330					335	
Glu	Val	Gly	Gly	Ala	Ile	Tyr	Val	Phe	Met	Asn	Gln	Ala	Gly	Thr	Ser
			340					345					350		
Phe	Pro	Ala	His	Pro	Ser	Leu	Leu	Leu	His	Gly	Pro	Ser	Gly	Ser	Ala
		355					360					365			
Phe	Gly	Leu	Ser	Val	Ala	Ser	Ile	Gly	Asp	Ile	Asn	Gln	Asp	Gly	Phe
		370				375					380				
Gln	Asp	Ile	Ala	Val	Gly	Ala	Pro	Phe	Glu	Gly	Leu	Gly	Lys	Val	Tyr
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Ile	Tyr	His	Ser	Ser	Ser	Lys	Gly	Leu	Leu	Arg	Gln	Pro	Gln	Gln	Val
				405					410						415
Ile	His	Gly	Glu	Lys	Leu	Gly	Leu	Pro	Gly	Leu	Ala	Thr	Phe	Gly	Tyr
			420					425					430		
Ser	Leu	Ser	Gly	Gln	Met	Asp	Val	Asp	Glu	Asn	Phe	Tyr	Pro	Asp	Leu
			435				440					445			
Leu	Val	Gly	Ser	Leu	Ser	Asp	His	Ile	Val	Leu	Leu	Arg	Ala	Arg	Pro
		450				455					460				
Val	Ile	Asn	Ile	Val	His	Lys	Thr	Leu	Val	Pro	Arg	Pro	Ala	Val	Leu
465					470					475					480
Asp	Pro	Ala	Leu	Cys	Thr	Ala	Thr	Ser	Cys	Val	Gln	Val	Glu	Leu	Cys
				485					490					495	
Phe	Ala	Tyr	Asn	Gln	Ser	Ala	Gly	Asn	Pro	Asn	Tyr	Arg	Arg	Asn	Ile
			500					505					510		
Thr	Leu	Ala	Tyr	Thr	Leu	Glu	Ala	Asp	Arg	Asp	Arg	Arg	Pro	Pro	Arg
		515					520					525			
Leu	Arg	Phe	Ala	Gly	Ser	Glu	Ser	Ala	Val	Phe	His	Gly	Phe	Phe	Ser
		530				535					540				
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Pro	Leu	Arg	Met	Pro	Asp	Arg	Pro	Arg	Leu	Gly	Leu	Arg	Ser	Leu	Asp
			580					585					590		
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Arg Leu Gln Tyr Ser	Arg Asp Val Arg Lys Leu Leu Leu Ser Ile Asn			
	645		650	655
Val Thr Asn Thr Arg	Thr Ser Glu Arg Ser Gly Glu Asp Ala His Glu			
	660		665	670
Ala Leu Leu Thr Leu	Val Val Pro Pro Ala Leu Leu Leu Ser Ser Val			
	675		680	685
Arg Pro Pro Gly Ala	Cys Gln Ala Asn Glu Thr Ile Phe Cys Glu Leu			
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Gln Leu Ser Thr Ser	Ser His Gln Asp Asn Leu Trp Pro Met Ile Leu			
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Thr Leu Leu Val Asp	Tyr Thr Leu Gln Thr Ser Leu Ser Met Val Asn			
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Pro Thr Glu Ile Thr	Val His Gly Asn Gly Ser Trp Pro Cys Arg Pro			
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Asp Arg Pro Ser Ser	Pro Gln Arg Arg Arg Arg Gln Leu Asp Pro Gly			
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<211> 4495

<212> DNA

<213> Homo sapiens

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<212> PRT

<213> Homo sapiens

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Glu Thr Gly Met Cys Gln Leu Gly Thr Ser Gly Gly Phe Thr Gln Asn
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Asp Pro Glu Asp Gln Gly Asn Leu Tyr Ile Gly Tyr Thr Met Gln Val
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<212> PRT

<213> Homo sapiens

<400> 101

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Lys Glu Met Ser Lys Leu Thr Ser Asn Phe Arg Leu Gly Phe Gly Ser
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<212> DNA

<213> Homo sapiens

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<211> 408

<212> PRT

<213> Homo sapiens

<400> 105

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Ser	Gly	Ala	Ala	Glu	Gln	Lys	Tyr	Val	Glu	Lys	Phe	Leu	Arg	Val	His	50	55	60
Gly	Ile	Ser	Leu	Gln	Glu	Thr	Thr	Arg	Ala	Glu	Thr	Gly	Met	Ala	Tyr	65	70	75
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Leu	Arg	Asn	Glu	Gly	Val	Ser	Ser	Val	Leu	Leu	Gly	Ser	Ser	Thr	Pro	355	360	365
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<211> 3103

<212> DNA

<213> Homo sapiens

<400> 106

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<210> 107

<211> 419

<212> PRT

<213> Homo sapiens

<400> 107

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Lys Ser Pro	Lys Lys Ala Ser Glu Asn Ala Lys Asp Ser Ser Leu Ser					
	35	40				
Pro Ser Gly	Glu Ser Gln Leu Arg Ala Arg Gln Leu Ala Leu Leu Arg					
	50	55				
Glu Val Glu	Met Asn Trp Tyr Leu Lys Leu Cys Asp Leu Ser Ser Glu					
65	70	75				
His Thr Thr	Val Cys Thr Thr Gly Met Pro His Arg Asn Leu Gly Lys					
	85	90				
Ser Gly Leu	Arg Val Ser Cys Leu Gly Leu Gly Thr Trp Val Thr Phe					
	100	105				
Gly Gly Gln	Ile Ser Asp Glu Val Ala Glu Arg Leu Met Thr Ile Ala					
	115	120				
Tyr Glu Ser	Gly Val Asn Leu Phe Asp Thr Ala Glu Val Tyr Ala Ala					
	130	135				
Gly Lys Ala	Glu Val Ile Leu Gly Ser Ile Ile Lys Lys Lys Gly Trp					
145	150	155				
Arg Arg Ser	Ser Leu Val Ile Thr Thr Lys Leu Tyr Trp Gly Gly Lys					
	165	170				
Ala Glu Thr	Glu Arg Gly Leu Ser Arg Lys His Ile Ile Glu Gly Leu					
	180	185				
Lys Gly Ser	Leu Gln Arg Leu Gln Leu Glu Tyr Val Asp Val Val Phe					
	195	200				
Ala Asn Arg	Pro Asp Ser Asn Thr Pro Met Glu Glu Ile Val Arg Ala					
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Met Thr His	Val Ile Asn Gln Gly Met Ala Met Tyr Trp Gly Thr Ser					
225	230	235				
Arg Trp Ser	Ala Met Glu Ile Met Glu Ala Tyr Ser Val Ala Arg Gln					
	245	250				
Phe Asn Met	Ile Pro Pro Val Cys Glu Gln Ala Glu Tyr His Leu Phe					
	260	265				
Gln Arg Glu	Lys Val Glu Val Gln Leu Pro Glu Leu Tyr His Lys Ile					
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Gly Val Gly	Ala Met Thr Trp Ser Pro Leu Ala Cys Gly Ile Ile Ser					
	290	295				
Gly Lys Tyr	Gly Asn Gly Val Pro Glu Ser Ser Arg Ala Ser Leu Lys					
305	310	315				
Cys Tyr Gln	Trp Leu Lys Glu Arg Ile Val Ser Glu Glu Gly Arg Lys					
	325	330				
Gln Gln Asn	Lys Leu Lys Asp Leu Ser Pro Ile Ala Glu Arg Leu Gly					
	340	345				
Cys Thr Leu	Pro Gln Leu Ala Val Ala Trp Cys Leu Arg Asn Glu Gly					
	355	360				
Val Ser Ser	Val Leu Leu Gly Ser Ser Thr Pro Glu Gln Leu Ile Glu					
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<210> 108

<211> 2620

<212> DNA

<213> Homo sapiens

<400> 108

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<210> 109

<211> 401

<212> PRT

<213> Homo sapiens

<400> 109

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Val Asn Ala Ala Arg Ala Lys Phe Arg Thr Val Ala Ile Ile Ala Arg
      35              40              45

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Ser Leu Gly Thr Phe Thr Pro Gln His His Ile Ser Leu Lys Glu Ser
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 Thr Ala Lys Gln Thr Gly Met Lys Tyr Arg Asn Leu Gly Lys Ser Gly
 65 70 75 80
 Leu Arg Val Ser Cys Leu Gly Leu Gly Thr Trp Val Thr Phe Gly Gly
 85 90 95
 Gln Ile Ser Asp Glu Val Ala Glu Arg Leu Met Thr Ile Ala Tyr Glu
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 Ser Gly Val Asn Leu Phe Asp Thr Ala Glu Val Tyr Ala Ala Gly Lys
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 Ala Glu Val Ile Leu Gly Ser Ile Ile Lys Lys Lys Gly Trp Arg Arg
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 Ser Ser Leu Val Ile Thr Thr Lys Leu Tyr Trp Gly Gly Lys Ala Glu
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 Thr Glu Arg Gly Leu Ser Arg Lys His Ile Ile Glu Gly Leu Lys Gly
 165 170 175
 Ser Leu Gln Arg Leu Gln Leu Glu Tyr Val Asp Val Val Phe Ala Asn
 180 185 190
 Arg Pro Asp Ser Asn Thr Pro Met Glu Glu Ile Val Arg Ala Met Thr
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 His Val Ile Asn Gln Gly Met Ala Met Tyr Trp Gly Thr Ser Arg Trp
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 Ser Ala Met Glu Ile Met Glu Ala Tyr Ser Val Ala Arg Gln Phe Asn
 225 230 235 240
 Met Ile Pro Pro Val Cys Glu Gln Ala Glu Tyr His Leu Phe Gln Arg
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 Glu Lys Val Glu Val Gln Leu Pro Glu Leu Tyr His Lys Ile Gly Val
 260 265 270
 Gly Ala Met Thr Trp Ser Pro Leu Ala Cys Gly Ile Ile Ser Gly Lys
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 Tyr Gly Asn Gly Val Pro Glu Ser Ser Arg Ala Ser Leu Lys Cys Tyr
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 Gln Trp Leu Lys Glu Arg Ile Val Ser Glu Glu Gly Arg Lys Gln Gln
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 Asn Lys Leu Lys Asp Leu Ser Pro Ile Ala Glu Arg Leu Gly Cys Thr
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 Leu Pro Gln Leu Ala Val Ala Trp Cys Leu Arg Asn Glu Gly Val Ser
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 <212> DNA
 <213> Homo sapiens

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<211> 677

<212> PRT

<213> Homo sapiens

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Glu	Ala	Ile	Gln	Gly	Met	Leu	Ser	Met	Ala	Asn	Leu	Gln	Ala	Ser	Asp
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Ser	Cys	Leu	Gln	Thr	Thr	Trp	Gly	Ala	Gly	Gln	Ala	Lys	Gly	Ser	Ser
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 435 440 445
 Ser Asp Tyr Val Tyr Pro Ser Leu Glu Ser Asp Glu Asp Asn Pro Ile
 450 455 460
 Phe Lys Ser Arg Ser Lys Lys Arg Lys Gly Ser Asp Asp Ala Pro Tyr
 465 470 475 480
 Ser Pro Thr Ala Arg Val Gly Pro Ser Val Pro Arg Gln Asp Arg Pro
 485 490 495
 Val Arg Glu Gly Thr Arg Val Ala Ser Ile Glu Thr Gly Leu Ala Ala
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 Ala Ala Ala Lys Leu Ser Gln Gln Glu Glu Gln Lys Ser Lys Lys Lys
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 545 550 555 560
 Ser Thr Thr Pro Ala Ser Thr Thr Pro Ala Ser Thr Thr Pro Ala Ser
 565 570 575
 Thr Ser Thr Ala Ser Ser Gln Ala Ser Gln Glu Gly Ser Ser Pro Glu
 580 585 590
 Pro Pro Pro Glu Ser His Ser Ser Ser Leu Ala Asp His Glu Tyr Thr
 595 600 605
 Ala Ala Gly Thr Phe Thr Gly Ala Gln Ala Gly Arg Thr Ser Gln Pro
 610 615 620
 Met Ala Pro Gly Val Phe Leu Thr Gln Arg Arg Pro Ser Ala Ser Ser
 625 630 635 640
 Pro Asn Asn Asn Thr Ala Ala Lys Gly Lys Arg Thr Lys Lys Gly Met
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<210> 112

<211> 5433

<212> DNA

<213> Homo sapiens

<400> 112

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<211> 1713

<212> PRT

<213> Homo sapiens

<400> 113

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Val Pro Cys Asn Cys Asn Gly His Ser Asn Gln Cys Gln Asp Gly Ser
65          70          75          80
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85          90          95
Arg Cys Gln Glu Gly Tyr Tyr Gly Asn Ala Val His Gly Ser Cys Arg
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Gln Cys Glu Arg Cys Ala Pro Gly Tyr Phe Gly Asn Pro Gln Lys Phe
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Ser Cys His Pro Leu Thr Gly Asp Cys Ile Asn Gln Glu Pro Lys Asp
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Ser Ser Pro Ala Glu Glu Cys Asp Asp Cys Asp Ser Cys Val Met Thr
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Ser Gln Leu Gln Gly Leu Ser Ala Ser Ala Gly Leu Leu Glu Gln Met
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Arg Glu Leu Thr Asp Leu Asn Gln Glu Phe Glu Thr Leu Gln Glu Lys

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Arg Lys Ala Asn Asp Ile Thr	Asp Glu Val Leu Asp	Gly Leu Asn Pro
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His Leu Cys Val Tyr Leu Glu Ala Gly Lys Val Thr Ala Ser Met Asp	1585	1590	1595
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Pro Ala Asn Leu Thr Thr Leu Arg Ile Pro Val Trp Lys Ser Phe Phe	1665	1670	1675
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<210> 114
 <211> 5175
 <212> DNA
 <213> Homo sapiens

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<211> 1193

<212> PRT

<213> Homo sapiens

<400> 115

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Asn Gly Phe Arg Cys Leu Asn Cys Asn Asp Asn Thr Asp Gly Ile His
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Cys Glu Lys Cys Lys Asn Gly Phe Tyr Arg His Arg Glu Arg Asp Arg
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<212> DNA

<213> Homo sapiens

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Pro Pro Lys Glu Thr Pro Lys Lys Lys Lys Lys Phe Ser Phe Lys Lys
85 90 95
Pro Phe Lys Leu Ser Gly Leu Ser Phe Lys Arg Asn Arg Lys Glu Gly
100 105 110
Gly Gly Asp Ser Ser Ala Ser Ser Pro Thr Glu Glu Glu Gln Glu Gln
115 120 125
Gly Glu Ile Gly Ala Cys Ser Asp Glu Gly Thr Ala Gln Glu Gly Lys
130 135 140
Ala Ala Ala Thr Pro Glu Ser Gln Glu Pro Gln Ala Lys Gly Ala Glu
145 150 155 160
Ala Ser Ala Ala Ser Glu Glu Glu Ala Gly Pro Gln Ala Thr Glu Pro
165 170 175
Ser Thr Pro Ser Gly Pro Glu Ser Gly Pro Thr Pro Ala Ser Ala Glu
180 185 190
Gln Asn Glu
195

<210> 122
<211> 1081
<212> DNA
<213> Homo sapiens

<400> 122
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ctggaccgc tgccgccgtt ccctgaccac gtccagtaca ccactatag cgaccagatc 240
gacaaccag actactatga ttatcaagag gtgactcctc ggccctccga ggaacagttc 300
cagttccagt ccagcagca agtccaacag gaagtcattc cagccccaac ccagaacca 360
ggaaatgcag agctggagcc cacagagcct gggcctcttg actgccgtga ggaacagtac 420
ccgtgcaccc gcctctactc catacacagg ccttgcaaac agtgtctcaa cgaggctctgc 480
ttctacagcc tccgccgtgt gtacgtcatt aacaaggaga tctgtgttcg tacagtgtgt 540
gcccacgagg agctcctccg agctgacctc tgtcgggaca agttctccaa atgtggcgtg 600
atggcagca gcggcctgtg ccaatccgtg gggcctcct gtgccaggag ctgtgggagc 660
tgtagggtg gtgctggcat cctgagtcct ggcctcctg ggatctggg ccctcgggct 720
acctgacctg gtgctttttt ccccatcccc atgttccttt tattctgaaa aagttagttg 780
actgcagccc tgggggttgc aggtgcggt gcctcaggcc cctccttcag cctgtggcca 840
cctctggggc acgatgggg ctccccactg ccagtcctgc ccctcgggtt gggggagtat 900
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acagtccccc gaggttagct acatcccccc accccagctg gtctgcttgg atttcctaca 1020
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 a 1081

<210> 123
 <211> 183
 <212> PRT
 <213> Homo sapiens

<400> 123
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 Val Gln Tyr Thr His Tyr Ser Asp Gln Ile Asp Asn Pro Asp Tyr Tyr
 35 40 45
 Asp Tyr Gln Glu Val Thr Pro Arg Pro Ser Glu Glu Gln Phe Gln Phe
 50 55 60
 Gln Ser Gln Gln Gln Val Gln Gln Glu Val Ile Pro Ala Pro Thr Pro
 65 70 75 80
 Glu Pro Gly Asn Ala Glu Leu Glu Pro Thr Glu Pro Gly Pro Leu Asp
 85 90 95
 Cys Arg Glu Glu Gln Tyr Pro Cys Thr Arg Leu Tyr Ser Ile His Arg
 100 105 110
 Pro Cys Lys Gln Cys Leu Asn Glu Val Cys Phe Tyr Ser Leu Arg Arg
 115 120 125
 Val Tyr Val Ile Asn Lys Glu Ile Cys Val Arg Thr Val Cys Ala His
 130 135 140
 Glu Glu Leu Leu Arg Ala Asp Leu Cys Arg Asp Lys Phe Ser Lys Cys
 145 150 155 160
 Gly Val Met Ala Ser Ser Gly Leu Cys Gln Ser Val Ala Ala Ser Cys
 165 170 175
 Ala Arg Ser Cys Gly Ser Cys
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<210> 124
 <211> 1066
 <212> DNA
 <213> Homo sapiens

<400> 124
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 ctgctattcc tgcctgcagg cttgctggct cagggccagt atgatctgga ccgctgccg 180
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 cagcaagtcc aacaggaagt catcccagcc ccaaccccag aaccaggaaa tgcagagctg 360
 gagcccacag agcctgggcc tcttgactgc cgtgaggaac agtaccctg caccgcctc 420
 tactccatac acaggccttg caaacagtgt ctcaacgagg tctgcttcta cagcctccgc 480
 cgtgtgtacg tcattaacaa ggagatctgt gttcgtacag tgtgtgcca cgaggagctc 540
 ctccgagctg acctctgtcg ggacaagtgc tccaaatgtg gcgtgatggc cagcagcggc 600
 ctgtgccaat ccgtggcggc ctccctgtgcc aggagctgtg ggagctgcta gggtggtgct 660
 ggcatacctga gtcctggccc tcctgggata tggggccctc gggctacctg acctgggtgct 720
 tttttcccca tcccattgtt ccttttattc tgaaaaagtt agtggactgc agccctgggg 780
 gttgcaggct cgggtgcctc agggccctcc ttcagcctgt ggccacctc ggggcacgat 840
 gggggctccc cactgccag tctgccctc gggttggggg agtatccag gcctctctgt 900
 gggacctggg cctgacgggc ccttctcagc ccgttttgag gacagacagt cccccagggt 960
 aggctacatc cccccacccc agctgggtctg cttggatttc ctacagcccc cgtgggcatg 1020

gaccaccttt attttatataca aaattaaaaa caagttttta caaaaa

1066

<210> 125

<211> 183

<212> PRT

<213> Homo sapiens

<400> 125

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          20           25           30
Val Gln Tyr Thr His Tyr Ser Asp Gln Ile Asp Asn Pro Asp Tyr Tyr
          35           40           45
Asp Tyr Gln Glu Val Thr Pro Arg Pro Ser Glu Glu Gln Phe Gln Phe
          50           55           60
Gln Ser Gln Gln Gln Val Gln Gln Glu Val Ile Pro Ala Pro Thr Pro
          65           70           75           80
Glu Pro Gly Asn Ala Glu Leu Glu Pro Thr Glu Pro Gly Pro Leu Asp
          85           90           95
Cys Arg Glu Glu Gln Tyr Pro Cys Thr Arg Leu Tyr Ser Ile His Arg
          100          105          110
Pro Cys Lys Gln Cys Leu Asn Glu Val Cys Phe Tyr Ser Leu Arg Arg
          115          120          125
Val Tyr Val Ile Asn Lys Glu Ile Cys Val Arg Thr Val Cys Ala His
          130          135          140
Glu Glu Leu Leu Arg Ala Asp Leu Cys Arg Asp Lys Phe Ser Lys Cys
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Gly Val Met Ala Ser Ser Gly Leu Cys Gln Ser Val Ala Ala Ser Cys
          165          170          175
Ala Arg Ser Cys Gly Ser Cys
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<210> 126

<211> 1611

<212> DNA

<213> Homo sapiens

<400> 126

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tgggtgtgag cagcaggcag gcaggcaatc ggtccgagtg gctgtcggct cttcagctct 180
ccgctcggcg tcttccttcc tctcccggtc agcgtcggcg gctgcaccgg cggcgggcag 240
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ggcgaggggc cctacggcat ggtgtgctct gcttatgata atgtcaacaa agttcgagta 480
gctatcaaga aaatcagccc ctttgagcac cagacctact gccagagaac cctgagggag 540
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gcaccaacca tcgagcaaat gaaagatgta tatatagtag aggacctcat ggaaacagat 660
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cagatcctca gaggggttaa atatatccat tcagctaacy ttctgcaccg tgacctcaag 780
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<210> 127
<211> 360
<212> PRT
<213> Homo sapiens
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			20					25					30		
Glu	Gly	Ala	Tyr	Gly	Met	Val	Cys	Ser	Ala	Tyr	Asp	Asn	Val	Asn	Lys
		35					40					45			
Val	Arg	Val	Ala	Ile	Lys	Lys	Ile	Ser	Pro	Phe	Glu	His	Gln	Thr	Tyr
	50					55					60				
Cys	Gln	Arg	Thr	Leu	Arg	Glu	Ile	Lys	Ile	Leu	Leu	Arg	Phe	Arg	His
65					70					75					80
Glu	Asn	Ile	Ile	Gly	Ile	Asn	Asp	Ile	Ile	Arg	Ala	Pro	Thr	Ile	Glu
				85					90					95	
Gln	Met	Lys	Asp	Val	Tyr	Ile	Val	Gln	Asp	Leu	Met	Glu	Thr	Asp	Leu
			100					105					110		
Tyr	Lys	Leu	Leu	Lys	Thr	Gln	His	Leu	Ser	Asn	Asp	His	Ile	Cys	Tyr
		115					120					125			
Phe	Leu	Tyr	Gln	Ile	Leu	Arg	Gly	Leu	Lys	Tyr	Ile	His	Ser	Ala	Asn
	130					135					140				
Val	Leu	His	Arg	Asp	Leu	Lys	Pro	Ser	Asn	Leu	Leu	Leu	Asn	Thr	Thr
145					150					155					160
Cys	Asp	Leu	Lys	Ile	Cys	Asp	Phe	Gly	Leu	Ala	Arg	Val	Ala	Asp	Pro
				165					170					175	
Asp	His	Asp	His	Thr	Gly	Phe	Leu	Thr	Glu	Tyr	Val	Ala	Thr	Arg	Trp
			180					185					190		
Tyr	Arg	Ala	Pro	Glu	Ile	Met	Leu	Asn	Ser	Lys	Gly	Tyr	Thr	Lys	Ser
		195					200					205			
Ile	Asp	Ile	Trp	Ser	Val	Gly	Cys	Ile	Leu	Ala	Glu	Met	Leu	Ser	Asn
	210					215					220				
Arg	Pro	Ile	Phe	Pro	Gly	Lys	His	Tyr	Leu	Asp	Gln	Leu	Asn	His	Ile
225					230					235					240
Leu	Gly	Ile	Leu	Gly	Ser	Pro	Ser	Gln	Glu	Asp	Leu	Asn	Cys	Ile	Ile
				245					250					255	
Asn	Leu	Lys	Ala	Arg	Asn	Tyr	Leu	Leu	Ser	Leu	Pro	His	Lys	Asn	Lys
			260					265					270		
Val	Pro	Trp	Asn	Arg	Leu	Phe	Pro	Asn	Ala	Asp	Ser	Lys	Ala	Leu	Asp
		275					280					285			
Leu	Leu	Asp	Lys	Met	Leu	Thr	Phe	Asn	Pro	His	Lys	Arg	Ile	Glu	Val
	290					295					300				
Glu	Gln	Ala	Leu	Ala	His	Pro	Tyr	Leu	Glu	Gln	Tyr	Tyr	Asp	Pro	Ser
305					310					315					320
Asp	Glu	Pro	Ile	Ala	Glu	Ala	Pro	Phe	Lys	Phe	Asp	Met	Glu	Leu	Asp
				325					330					335	
Asp	Leu	Pro	Lys	Glu	Lys	Leu	Lys	Glu	Leu	Ile	Phe	Glu	Glu	Thr	Ala
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Arg Phe Gln Pro Gly Tyr Arg Ser
355 360

<210> 128
<211> 2917
<212> DNA
<213> Homo sapiens

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tggtgatttt caaaagggtc gtattcaaga gacccaagct gagcttcctc gagggagtat 720
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<210> 129
 <211> 821
 <212> PRT
 <213> Homo sapiens

<400> 129

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			20					25					30		
Phe	Leu	Glu	Glu	Phe	Gln	Ser	Ser	Asp	Gly	Glu	Ile	Lys	Tyr	Leu	Gln
			35				40					45			
Leu	Ala	Glu	Glu	Leu	Ile	Arg	Pro	Glu	Arg	Asn	Thr	Leu	Val	Val	Ser
	50					55					60				
Phe	Val	Asp	Leu	Glu	Gln	Phe	Asn	Gln	Gln	Leu	Ser	Thr	Thr	Ile	Gln
65					70					75					80
Glu	Glu	Phe	Tyr	Arg	Val	Tyr	Pro	Tyr	Leu	Cys	Arg	Ala	Leu	Lys	Thr
				85					90					95	
Phe	Val	Lys	Asp	Arg	Lys	Glu	Ile	Pro	Leu	Ala	Lys	Asp	Phe	Tyr	Val
			100					105					110		
Ala	Phe	Gln	Asp	Leu	Pro	Thr	Arg	His	Lys	Ile	Arg	Glu	Leu	Thr	Ser
		115					120					125			
Ser	Arg	Ile	Gly	Leu	Leu	Thr	Arg	Ile	Ser	Gly	Gln	Val	Val	Arg	Thr
	130					135					140				
His	Pro	Val	His	Pro	Glu	Leu	Val	Ser	Gly	Thr	Phe	Leu	Cys	Leu	Asp
145					150					155					160
Cys	Gln	Thr	Val	Ile	Arg	Asp	Val	Glu	Gln	Gln	Phe	Lys	Tyr	Thr	Gln
				165					170						175
Pro	Asn	Ile	Cys	Arg	Asn	Pro	Val	Cys	Ala	Asn	Arg	Arg	Arg	Phe	Leu
			180					185					190		
Leu	Asp	Thr	Asn	Lys	Ser	Arg	Phe	Val	Asp	Phe	Gln	Lys	Val	Arg	Ile
	195						200					205			
Gln	Glu	Thr	Gln	Ala	Glu	Leu	Pro	Arg	Gly	Ser	Ile	Pro	Arg	Ser	Leu
	210					215						220			
Glu	Val	Ile	Leu	Arg	Ala	Glu	Ala	Val	Glu	Ser	Ala	Gln	Ala	Gly	Asp
225					230					235					240
Lys	Cys	Asp	Phe	Thr	Gly	Thr	Leu	Ile	Val	Val	Pro	Asp	Val	Ser	Lys
			245						250					255	
Leu	Ser	Thr	Pro	Gly	Ala	Arg	Ala	Glu	Thr	Asn	Ser	Arg	Val	Ser	Gly
		260						265					270		
Val	Asp	Gly	Tyr	Glu	Thr	Glu	Gly	Ile	Arg	Gly	Leu	Arg	Ala	Leu	Gly
		275					280					285			
Val	Arg	Asp	Leu	Ser	Tyr	Arg	Leu	Val	Phe	Leu	Ala	Cys	Cys	Val	Ala
	290					295					300				
Pro	Thr	Asn	Pro	Arg	Phe	Gly	Gly	Lys	Glu	Leu	Arg	Asp	Glu	Glu	Gln
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Thr	Ala	Glu	Ser	Ile	Lys	Asn	Gln	Met	Thr	Val	Lys	Glu	Trp	Glu	Lys
			325						330					335	
Val	Phe	Glu	Met	Ser	Gln	Asp	Lys	Asn	Leu	Tyr	His	Asn	Leu	Cys	Thr
			340					345					350		
Ser	Leu	Phe	Pro	Thr	Ile	His	Gly	Asn	Asp	Glu	Val	Lys	Arg	Gly	Val
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Leu	Leu	Met	Leu	Phe	Gly	Gly	Val	Pro	Lys	Thr	Thr	Gly	Glu	Gly	Thr
		370				375					380				
Ser	Leu	Arg	Gly	Asp	Ile	Asn	Val	Cys	Ile	Val	Gly	Asp	Pro	Ser	Thr
385					390					395					400
Ala	Lys	Ser	Gln	Phe	Leu	Lys	His	Val	Glu	Glu	Phe	Ser	Pro	Arg	Ala
				405					410					415	

Val	Tyr	Thr	Ser	Gly	Lys	Ala	Ser	Ser	Ala	Ala	Gly	Leu	Thr	Ala	Ala		
			420					425					430				
Val	Val	Arg	Asp	Glu	Glu	Ser	His	Glu	Phe	Val	Ile	Glu	Ala	Gly	Ala		
		435					440					445					
Leu	Met	Leu	Ala	Asp	Asn	Gly	Val	Cys	Cys	Ile	Asp	Glu	Phe	Asp	Lys		
	450					455					460						
Met	Asp	Val	Arg	Asp	Gln	Val	Ala	Ile	His	Glu	Ala	Met	Glu	Gln	Gln		
465					470					475					480		
Thr	Ile	Ser	Ile	Thr	Lys	Ala	Gly	Val	Lys	Ala	Thr	Leu	Asn	Ala	Arg		
			485						490					495			
Thr	Ser	Ile	Leu	Ala	Ala	Ala	Asn	Pro	Ile	Ser	Gly	His	Tyr	Asp	Arg		
			500					505					510				
Ser	Lys	Ser	Leu	Lys	Gln	Asn	Ile	Asn	Leu	Ser	Ala	Pro	Ile	Met	Ser		
		515					520					525					
Arg	Phe	Asp	Leu	Phe	Phe	Ile	Leu	Val	Asp	Glu	Cys	Asn	Glu	Val	Thr		
	530					535					540						
Asp	Tyr	Ala	Ile	Ala	Arg	Arg	Ile	Val	Asp	Leu	His	Ser	Arg	Ile	Glu		
545					550					555					560		
Glu	Ser	Ile	Asp	Arg	Val	Tyr	Ser	Leu	Asp	Asp	Ile	Arg	Arg	Tyr	Leu		
			565						570					575			
Leu	Phe	Ala	Arg	Gln	Phe	Lys	Pro	Lys	Ile	Ser	Lys	Glu	Ser	Glu	Asp		
			580					585					590				
Phe	Ile	Val	Glu	Gln	Tyr	Lys	His	Leu	Arg	Gln	Arg	Asp	Gly	Ser	Gly		
		595					600					605					
Val	Thr	Lys	Ser	Ser	Trp	Arg	Ile	Thr	Val	Arg	Gln	Leu	Glu	Ser	Met		
	610					615					620						
Ile	Arg	Leu	Ser	Glu	Ala	Met	Ala	Arg	Met	His	Cys	Cys	Asp	Glu	Val		
625					630					635					640		
Gln	Pro	Lys	His	Val	Lys	Glu	Ala	Phe	Arg	Leu	Leu	Asn	Lys	Ser	Ile		
			645					650					655				
Ile	Arg	Val	Glu	Thr	Pro	Asp	Val	Asn	Leu	Asp	Gln	Glu	Glu	Glu	Ile		
			660					665					670				
Gln	Met	Glu	Val	Asp	Glu	Gly	Ala	Gly	Gly	Ile	Asn	Gly	His	Ala	Asp		
		675					680					685					
Ser	Pro	Ala	Pro	Val	Asn	Gly	Ile	Asn	Gly	Tyr	Asn	Glu	Asp	Ile	Asn		
	690					695					700						
Gln	Glu	Ser	Ala	Pro	Lys	Ala	Ser	Leu	Arg	Leu	Gly	Phe	Ser	Glu	Tyr		
705					710					715					720		
Cys	Arg	Ile	Ser	Asn	Leu	Ile	Val	Leu	His	Leu	Arg	Lys	Val	Glu	Glu		
				725						730				735			
Glu	Glu	Asp	Glu	Ser	Ala	Leu	Lys	Arg	Ser	Glu	Leu	Val	Asn	Trp	Tyr		
			740					745					750				
Leu	Lys	Glu	Ile	Glu	Ser	Glu	Ile	Asp	Ser	Glu	Glu	Glu	Leu	Ile	Asn		
		755					760					765					
Lys	Lys	Arg	Ile	Ile	Glu	Lys	Val	Ile	His	Arg	Leu	Thr	His	Tyr	Asp		
		770				775					780						
His	Val	Leu	Ile	Glu	Leu	Thr	Gln	Ala	Gly	Leu	Lys	Gly	Ser	Thr	Glu		
785					790					795					800		
Gly	Ser	Glu	Ser	Tyr	Glu	Glu	Asp	Pro	Tyr	Leu	Val	Val	Asn	Pro	Asn		
				805					810					815			
Tyr	Leu	Leu	Glu	Asp													
			820														

<210> 130

<211> 786

<212> DNA

<213> Homo sapiens

<400> 130

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ccccgggagc gagtgcgctg agtgggectg ggggccctgc acccccagca gcaaggattg 180
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tgcgtgtgat gggggcacag gcaccaaagt ccgccaaggc accctgaaga aggcgcgcta 360
caatgctcag tgccaggaga ccatccgct caccaagccc tgcaccccca agaccaaagc 420
aaaggccaaa gccaaagaaag ggaagggaaa ggactagacg ccaagcctgg atgccaagga 480
gcccctggtg tcacatgggg cctggccacg ccctccctct ccaggcccg agatgtgacc 540
caccagtgc ttctgtctgc tcgttagctt taatcaatca tgccctgcct tgtccctctc 600
actccccagc cccacccta agtgcccaaa gtggggaggg acaagggtt ctgggaagct 660
tgagcctccc ccaaagcaat gtgagtccca gagcccgctt ttgttcttcc ccacaattcc 720
attactaaga aacacatcaa ataaactgac tttttccccc caataaaagc tcttcttttt 780
taatat 786

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<210> 131

<211> 143

<212> PRT

<213> Homo sapiens

<400> 131

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20           25           30
Pro Gly Ser Glu Cys Ala Glu Trp Ala Trp Gly Pro Cys Thr Pro Ser
35           40           45
Ser Lys Asp Cys Gly Val Gly Phe Arg Glu Gly Thr Cys Gly Ala Gln
50           55           60
Thr Gln Arg Ile Arg Cys Arg Val Pro Cys Asn Trp Lys Lys Glu Phe
65           70           75           80
Gly Ala Asp Cys Lys Tyr Lys Phe Glu Asn Trp Gly Ala Cys Asp Gly
85           90           95
Gly Thr Gly Thr Lys Val Arg Gln Gly Thr Leu Lys Lys Ala Arg Tyr
100          105          110
Asn Ala Gln Cys Gln Glu Thr Ile Arg Val Thr Lys Pro Cys Thr Pro
115          120          125
Lys Thr Lys Ala Lys Ala Lys Ala Lys Lys Gly Lys Gly Lys Asp
130          135          140

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<210> 132

<211> 603

<212> DNA

<213> Homo sapiens

<400> 132

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catggaatct tatgaactta atcccttcat taacaggaga aatgcaaata ccttcatatc 180
ccctcagcag agatggagag cttaaagtcca agagaggatc cgagaacgct ctaagcctgt 240
ccacgagctc aatagggaag cctgtgatga ctacagactt tgcgaacgct acgccatggt 300
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ctgaggggaag aaaaaaaatc tctttttttc tggaggctgg cacctgattt tgatatcccc 420
tgtagcagca ttactgaaat acataggctt atatacaatg cttcttttcc gtatatcttc 480
ttgtctggct gcaccccttt tcccccccc cagattgata agtaatgaaa gtgcactgca 540
gtgaggggtc aaggagagtc aacatatgtg attgttccat aataaacttc tgggtgtgata 600
ctt 603

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<210> 133
 <211> 103
 <212> PRT
 <213> Homo sapiens

<400> 133
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 20 25 30
 Pro Phe Ile Asn Arg Arg Asn Ala Asn Thr Phe Ile Ser Pro Gln Gln
 35 40 45
 Arg Trp Arg Ala Lys Val Gln Glu Arg Ile Arg Glu Arg Ser Lys Pro
 50 55 60
 Val His Glu Leu Asn Arg Glu Ala Cys Asp Asp Tyr Arg Leu Cys Glu
 65 70 75 80
 Arg Tyr Ala Met Val Tyr Gly Tyr Asn Ala Ala Tyr Asn Arg Tyr Phe
 85 90 95
 Arg Lys Arg Arg Gly Ala Lys
 100

<210> 134
 <211> 1778
 <212> DNA
 <213> Homo sapiens

<400> 134
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 ttagaaaaat tttatggcct tgagataaac aaacttccag tgacaaaaat gaaatatagt 180
 ggaaacttaa tgaaggaaaa aatccaagaa atgcagcact tcttgggtct gaaagtgacc 240
 gggcaactgg acacatctac cctggagatg atgcacgcac ctcgatgtgg agtccccgat 300
 ctccatcatt tcagggaat gccagggggg cccgtatgga ggaaacatta tatcacctac 360
 agaatcaata attacacacc tgacatgaac cgtgaggatg ttgactacgc aatccggaaa 420
 gctttccaag tatggagtaa tgttaccccc ttgaaattca gcaagattaa cacaggcatg 480
 gctgacattt tgggtggttt tgcccgtgga gctcatggag acttccatgc ttttgatggc 540
 aaaggtggaa tcctagccca tgcttttgga cctggatctg gcattggaag ggatgcacat 600
 ttcgatgagg acgaattctg gactacacat tcaggaggca caaacttgtt cctcactgct 660
 gttcacgaga ttggccattc cttaggtctt ggccattcta gtgatccaaa ggctgtaagt 720
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 ggcattcagt ccctgtatgg agacccaaaa gagaaccaac gcttgccaaa tcctgacaat 840
 tcagaaccag ctctctgtga cccaatttg agttttgatg ctgtcactac cgtgggaaat 900
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 gataaccagt attggaggta tgatgaaagg agacagatga tggaccctgg ttatcccaa 1260
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 cgtatcacca aaacactgaa aagcaatagc tggtttggtt gttagaaatg gtgtaattaa 1440
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 ctctgtaagt tgcttcctaa catccttgga ctgagaaatt atacttactt ctggcataac 1740
 taaaattaag tataatatatt ttggctcaaa taaaattg 1778

Met 1	Lys	Phe	Leu	Leu 5	Ile	Leu	Leu	Leu	Gln 10	Ala	Thr	Ala	Ser	Gly 15	Ala
Leu	Pro	Leu	Asn 20	Ser	Ser	Thr	Ser	Leu 25	Glu	Lys	Asn	Asn 30	Val	Leu	Phe
Gly	Glu	Arg 35	Tyr	Leu	Glu	Lys	Phe 40	Tyr	Gly	Leu	Glu	Ile 45	Asn	Lys	Leu
Pro	Val 50	Thr	Lys	Met	Lys	Tyr 55	Ser	Gly	Asn	Leu	Met 60	Lys	Glu	Lys	Ile
Gln 65	Glu	Met	Gln	His	Phe 70	Leu	Gly	Leu	Lys	Val 75	Thr	Gly	Gln	Leu	Asp 80
Thr	Ser	Thr	Leu 85	Glu	Met	Met	His	Ala	Pro 90	Arg	Cys	Gly	Val	Pro 95	Asp
Leu	His	His	Phe 100	Arg	Glu	Met	Pro	Gly 105	Gly	Pro	Val	Trp	Arg 110	Lys	His
Tyr	Ile	Thr	Tyr 115	Arg	Ile	Asn	Asn 120	Tyr	Thr	Pro	Asp	Met 125	Asn	Arg	Glu
Asp	Val 130	Asp	Tyr	Ala	Ile	Arg 135	Lys	Ala	Phe	Gln	Val 140	Trp	Ser	Asn	Val
Thr 145	Pro	Leu	Lys	Phe	Ser 150	Lys	Ile	Asn	Thr	Gly 155	Met	Ala	Asp	Ile	Leu 160
Val	Val	Phe	Ala 165	Arg	Gly	Ala	His	Gly	Asp 170	Phe	His	Ala	Phe	Asp 175	Gly
Lys	Gly	Gly	Ile 180	Leu	Ala	His	Ala	Phe 185	Gly	Pro	Gly	Ser	Gly 190	Ile	Gly
Gly	Asp	Ala	His 195	Phe	Asp	Glu	Asp 200	Glu	Phe	Trp	Thr	Thr 205	His	Ser	Gly
Gly	Thr 210	Asn	Leu	Phe	Leu	Thr 215	Ala	Val	His	Glu	Ile 220	Gly	His	Ser	Leu
Gly 225	Leu	Gly	His	Ser	Ser 230	Asp	Pro	Lys	Ala	Val 235	Met	Phe	Pro	Thr	Tyr 240
Lys	Tyr	Val	Asp 245	Ile	Asn	Thr	Phe	Arg	Leu 250	Ser	Ala	Asp	Asp 255	Ile	Arg
Gly	Ile	Gln	Ser 260	Leu	Tyr	Gly	Asp	Pro 265	Lys	Glu	Asn	Gln	Arg 270	Leu	Pro
Asn	Pro	Asp 275	Asn	Ser	Glu	Pro	Ala 280	Leu	Cys	Asp	Pro	Asn 285	Leu	Ser	Phe
Asp	Ala 290	Val	Thr	Thr	Val	Gly 295	Asn	Lys	Ile	Phe	Phe 300	Phe	Lys	Asp	Arg
Phe 305	Phe	Trp	Leu	Lys	Val 310	Ser	Glu	Arg	Pro	Lys 315	Thr	Ser	Val	Asn	Leu 320
Ile	Ser	Ser	Leu 325	Trp	Pro	Thr	Leu	Pro	Ser 330	Gly	Ile	Glu	Ala	Ala 335	Tyr
Glu	Ile	Glu	Ala 340	Arg	Asn	Gln	Val	Phe 345	Leu	Phe	Lys	Asp	Asp 350	Lys	Tyr
Trp	Leu	Ile 355	Ser	Asn	Leu	Arg	Pro 360	Glu	Pro	Asn	Tyr	Pro 365	Lys	Ser	Ile
His	Ser 370	Phe	Gly	Phe	Pro	Asn 375	Phe	Val	Lys	Lys	Ile 380	Asp	Ala	Ala	Val
Phe 385	Asn	Pro	Arg	Phe	Tyr 390	Arg	Thr	Tyr	Phe	Phe 395	Val	Asp	Asn	Gln	Tyr 400
Trp	Arg	Tyr	Asp 405	Glu	Arg	Arg	Gln	Met	Met 410	Asp	Pro	Gly	Tyr	Pro 415	Lys

Leu Ile Thr Lys Asn Phe Gln Gly Ile Gly Pro Lys Ile Asp Ala Val
 420 425 430
 Phe Tyr Ser Lys Asn Lys Tyr Tyr Tyr Phe Phe Gln Gly Ser Asn Gln
 435 440 445
 Phe Glu Tyr Asp Phe Leu Leu Gln Arg Ile Thr Lys Thr Leu Lys Ser
 450 455 460
 Asn Ser Trp Phe Gly Cys
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<210> 136

<211> 1821

<212> DNA

<213> Homo sapiens

<400> 136

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aactactacg acctcaaaaa agatgtgaaa cagtttggtta ggagaaagga cagtggctcct 240
gttggttaaaa aaatccgaga aatgcagaag ttccttggat tggaggtgac ggggaagctg 300
gactccgaca ctctggagggt gatgcgcaag cccagggtgtg gagttcctga tgttgggtcac 360
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agacgatttg tcagttgttt t

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<210> 137

<211> 477

<212> PRT

<213> Homo sapiens

<400> 137

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 20 25 30
 Leu Val Gln Lys Tyr Leu Glu Asn Tyr Tyr Asp Leu Lys Lys Asp Val

		35				40					45					
Lys	Gln	Phe	Val	Arg	Arg	Lys	Asp	Ser	Gly	Pro	Val	Val	Lys	Lys	Ile	
	50					55					60					
Arg	Glu	Met	Gln	Lys	Phe	Leu	Gly	Leu	Glu	Val	Thr	Gly	Lys	Leu	Asp	
65					70					75					80	
Ser	Asp	Thr	Leu	Glu	Val	Met	Arg	Lys	Pro	Arg	Cys	Gly	Val	Pro	Asp	
				85					90					95		
Val	Gly	His	Phe	Arg	Thr	Phe	Pro	Gly	Ile	Pro	Lys	Trp	Arg	Lys	Thr	
			100					105					110			
His	Leu	Thr	Tyr	Arg	Ile	Val	Asn	Tyr	Thr	Pro	Asp	Leu	Pro	Lys	Asp	
			115				120					125				
Ala	Val	Asp	Ser	Ala	Val	Glu	Lys	Ala	Leu	Lys	Val	Trp	Glu	Glu	Val	
	130					135					140					
Thr	Pro	Leu	Thr	Phe	Ser	Arg	Leu	Tyr	Glu	Gly	Glu	Ala	Asp	Ile	Met	
145					150					155					160	
Ile	Ser	Phe	Ala	Val	Arg	Glu	His	Gly	Asp	Phe	Tyr	Pro	Phe	Asp	Gly	
				165					170					175		
Pro	Gly	Asn	Val	Leu	Ala	His	Ala	Tyr	Ala	Pro	Gly	Pro	Gly	Ile	Asn	
			180					185					190			
Gly	Asp	Ala	His	Phe	Asp	Asp	Asp	Glu	Gln	Trp	Thr	Lys	Asp	Thr	Thr	
		195				200						205				
Gly	Thr	Asn	Leu	Phe	Leu	Val	Ala	Ala	His	Glu	Ile	Gly	His	Ser	Leu	
	210					215					220					
Gly	Leu	Phe	His	Ser	Ala	Asn	Thr	Glu	Ala	Leu	Met	Tyr	Pro	Leu	Tyr	
225					230					235					240	
His	Ser	Leu	Thr	Asp	Leu	Thr	Arg	Phe	Arg	Leu	Ser	Gln	Asp	Asp	Ile	
				245					250					255		
Asn	Gly	Ile	Gln	Ser	Leu	Tyr	Gly	Pro	Pro	Pro	Asp	Ser	Pro	Glu	Thr	
			260					265					270			
Pro	Leu	Val	Pro	Thr	Glu	Pro	Val	Pro	Pro	Glu	Pro	Gly	Thr	Pro	Ala	
		275					280					285				
Asn	Cys	Asp	Pro	Ala	Leu	Ser	Phe	Asp	Ala	Val	Ser	Thr	Leu	Arg	Gly	
	290					295				300						
Glu	Ile	Leu	Ile	Phe	Lys	Asp	Arg	His	Phe	Trp	Arg	Lys	Ser	Leu	Arg	
305					310					315					320	
Lys	Leu	Glu	Pro	Glu	Leu	His	Leu	Ile	Ser	Ser	Phe	Trp	Pro	Ser	Leu	
				325					330					335		
Pro	Ser	Gly	Val	Asp	Ala	Ala	Tyr	Glu	Val	Thr	Ser	Lys	Asp	Leu	Val	
			340					345					350			
Phe	Ile	Phe	Lys	Gly	Asn	Gln	Phe	Trp	Ala	Ile	Arg	Gly	Asn	Glu	Val	
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<210> 138
<211> 1127

<212> DNA

<213> Homo sapiens

<400> 138

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gaggcatgag tgagctacag tgggaacagg ctcaggacta tctcaagaga ttttatctct 180
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ccagatgttg agtgccagat gttgcagaat actcactatt tccaaatagc ccaaaatgga 360
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<210> 139

<211> 267

<212> PRT

<213> Homo sapiens

<400> 139

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20          25          30
Glu Gln Ala Gln Asp Tyr Leu Lys Arg Phe Tyr Leu Tyr Asp Ser Glu
35          40          45
Thr Lys Asn Ala Asn Ser Leu Glu Ala Lys Leu Lys Glu Met Gln Lys
50          55          60
Phe Phe Gly Leu Pro Ile Thr Gly Met Leu Asn Ser Arg Val Ile Glu
65          70          75          80
Ile Met Gln Lys Pro Arg Cys Gly Val Pro Asp Val Ala Glu Tyr Ser
85          90          95
Leu Phe Pro Asn Ser Pro Lys Trp Thr Ser Lys Val Val Thr Tyr Arg
100         105         110
Ile Val Ser Tyr Thr Arg Asp Leu Pro His Ile Thr Val Asp Arg Leu
115         120         125
Val Ser Lys Ala Leu Asn Met Trp Gly Lys Glu Ile Pro Leu His Phe
130         135         140
Arg Lys Val Val Trp Gly Thr Ala Asp Ile Met Ile Gly Phe Ala Arg
145         150         155         160
Gly Ala His Gly Asp Ser Tyr Pro Phe Asp Gly Pro Gly Asn Thr Leu
165         170         175
Ala His Ala Phe Ala Pro Gly Thr Gly Leu Gly Gly Asp Ala His Phe
180         185         190
Asp Glu Asp Glu Arg Trp Thr Asp Gly Ser Ser Leu Gly Ile Asn Phe
195         200         205
Leu Tyr Ala Ala Thr His Glu Leu Gly His Ser Leu Gly Met Gly His
210         215         220
Ser Ser Asp Pro Asn Ala Val Met Tyr Pro Thr Tyr Gly Asn Gly Asp

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225	230	235	240
Pro Gln Asn Phe Lys	Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Lys		
245	250	255	
Leu Tyr Gly Lys Arg Ser Asn Ser Arg Lys Lys			
260	265		

<210> 140
 <211> 1078
 <212> DNA
 <213> Homo sapiens

<400> 140

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tgggaacagg	ctcaggacta	tctcaagaga	ttttatctct	atgactcaga	aacaaaaaat	180
gccaacagtt	tagaagccaa	actcaaggag	atgcaaaaat	tctttggcct	acctataact	240
ggaatgttaa	actcccgctg	catagaaata	atgcagaagc	ccagatgtgg	agtgccagat	300
gttgacagaat	actcactatt	tccaaatagc	ccaaaatgga	cttccaaagt	ggtcacctac	360
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aaaggcaftc	agaaactata	tggaaagaga	agtaattcaa	gaaagaaata	gaaacttcag	840
gcagaacatc	cattcattca	ttcattggat	tgtatatcat	tgttgacaaa	tcagaattga	900
taagcactgt	tctcactctc	catttagcaa	ttatgtcacc	cttttttatt	gcagtgggtt	960
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<210> 141
 <211> 2334
 <212> DNA
 <213> Homo sapiens

<400> 141

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<210> 142

<211> 707

<212> PRT

<213> Homo sapiens

<400> 142

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  20          25          30
Gly Asp Leu Arg Thr Asn Leu Thr Asp Arg Gln Leu Ala Glu Glu Tyr
  35          40          45
Leu Tyr Arg Tyr Gly Tyr Thr Arg Val Ala Glu Met Arg Gly Glu Ser
  50          55          60
Lys Ser Leu Gly Pro Ala Leu Leu Leu Leu Gln Lys Gln Leu Ser Leu
  65          70          75          80
Pro Glu Thr Gly Glu Leu Asp Ser Ala Thr Leu Lys Ala Met Arg Thr
  85          90          95
Pro Arg Cys Gly Val Pro Asp Leu Gly Arg Phe Gln Thr Phe Glu Gly
  100         105         110
Asp Leu Lys Trp His His His Asn Ile Thr Tyr Trp Ile Gln Asn Tyr
  115         120         125
Ser Glu Asp Leu Pro Arg Ala Val Ile Asp Asp Ala Phe Ala Arg Ala
  130         135         140
Phe Ala Leu Trp Ser Ala Val Thr Pro Leu Thr Phe Thr Arg Val Tyr
  145         150         155         160
Ser Arg Asp Ala Asp Ile Val Ile Gln Phe Gly Val Ala Glu His Gly
  165         170         175
Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala His Ala Phe
  180         185         190
Pro Pro Gly Pro Gly Ile Gln Gly Asp Ala His Phe Asp Asp Asp Glu
  195         200         205
Leu Trp Ser Leu Gly Lys Gly Val Val Val Pro Thr Arg Phe Gly Asn
  210         215         220
Ala Asp Gly Ala Ala Cys His Phe Pro Phe Ile Phe Glu Gly Arg Ser
  225         230         235         240
Tyr Ser Ala Cys Thr Thr Asp Gly Arg Ser Asp Gly Leu Pro Trp Cys
  245         250         255
Ser Thr Thr Ala Asn Tyr Asp Thr Asp Asp Arg Phe Gly Phe Cys Pro
  260         265         270

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Ser Glu Arg Leu Tyr Thr Arg Asp Gly Asn Ala Asp Gly Lys Pro Cys
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 Gln Phe Pro Phe Ile Phe Gln Gly Gln Ser Tyr Ser Ala Cys Thr Thr
 290 295 300
 Asp Gly Arg Ser Asp Gly Tyr Arg Trp Cys Ala Thr Thr Ala Asn Tyr
 305 310 315 320
 Asp Arg Asp Lys Leu Phe Gly Phe Cys Pro Thr Arg Ala Asp Ser Thr
 325 330 335
 Val Met Gly Gly Asn Ser Ala Gly Glu Leu Cys Val Phe Pro Phe Thr
 340 345 350
 Phe Leu Gly Lys Glu Tyr Ser Thr Cys Thr Ser Glu Gly Arg Gly Asp
 355 360 365
 Gly Arg Leu Trp Cys Ala Thr Thr Ser Asn Phe Asp Ser Asp Lys Lys
 370 375 380
 Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val Ala Ala
 385 390 395 400
 His Glu Phe Gly His Ala Leu Gly Leu Asp His Ser Ser Val Pro Glu
 405 410 415
 Ala Leu Met Tyr Pro Met Tyr Arg Phe Thr Glu Gly Pro Pro Leu His
 420 425 430
 Lys Asp Asp Val Asn Gly Ile Arg His Leu Tyr Gly Pro Arg Pro Glu
 435 440 445
 Pro Glu Pro Arg Pro Pro Thr Thr Thr Pro Gln Pro Thr Ala Pro
 450 455 460
 Pro Thr Val Cys Pro Thr Gly Pro Pro Thr Val His Pro Ser Glu Arg
 465 470 475 480
 Pro Thr Ala Gly Pro Thr Gly Pro Pro Ser Ala Gly Pro Thr Gly Pro
 485 490 495
 Pro Thr Ala Gly Pro Ser Thr Ala Thr Thr Val Pro Leu Ser Pro Val
 500 505 510
 Asp Asp Ala Cys Asn Val Asn Ile Phe Asp Ala Ile Ala Glu Ile Gly
 515 520 525
 Asn Gln Leu Tyr Leu Phe Lys Asp Gly Lys Tyr Trp Arg Phe Ser Glu
 530 535 540
 Gly Arg Gly Ser Arg Pro Gln Gly Pro Phe Leu Ile Ala Asp Lys Trp
 545 550 555 560
 Pro Ala Leu Pro Arg Lys Leu Asp Ser Val Phe Glu Glu Pro Leu Ser
 565 570 575
 Lys Lys Leu Phe Phe Phe Ser Gly Arg Gln Val Trp Val Tyr Thr Gly
 580 585 590
 Ala Ser Val Leu Gly Pro Arg Arg Leu Asp Lys Leu Gly Leu Gly Ala
 595 600 605
 Asp Val Ala Gln Val Thr Gly Ala Leu Arg Ser Gly Arg Gly Lys Met
 610 615 620
 Leu Leu Phe Ser Gly Arg Arg Leu Trp Arg Phe Asp Val Lys Ala Gln
 625 630 635 640
 Met Val Asp Pro Arg Ser Ala Ser Glu Val Asp Arg Met Phe Pro Gly
 645 650 655
 Val Pro Leu Asp Thr His Asp Val Phe Gln Tyr Arg Glu Lys Ala Tyr
 660 665 670
 Phe Cys Gln Asp Arg Phe Tyr Trp Arg Val Ser Ser Arg Ser Glu Leu
 675 680 685
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 Pro Glu Asp
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<211> 2217
 <212> DNA
 <213> Homo sapiens

<400> 143

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<210> 144
 <211> 702
 <212> PRT
 <213> Homo sapiens

<400> 144

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             20             25             30
Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
             35             40             45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
             50             55             60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
             65             70             75             80

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Arg	Val	Arg	Glu	Leu	Ala	Val	Ala	Leu	Ala	Gln	Lys	Asn	Val	Lys	Leu	85	90	95
Ser	Thr	Glu	Gln	Leu	Arg	Cys	Leu	Ala	His	Arg	Leu	Ser	Glu	Pro	Pro	100	105	110
Glu	Asp	Leu	Asp	Ala	Leu	Pro	Leu	Asp	Leu	Leu	Leu	Phe	Leu	Asn	Pro	115	120	125
Asp	Ala	Phe	Ser	Gly	Pro	Gln	Ala	Cys	Thr	Arg	Phe	Phe	Ser	Arg	Ile	130	135	140
Thr	Lys	Ala	Asn	Val	Asp	Leu	Leu	Pro	Arg	Gly	Ala	Pro	Glu	Arg	Gln	145	150	155
Arg	Leu	Leu	Pro	Ala	Ala	Leu	Ala	Cys	Trp	Gly	Val	Arg	Gly	Ser	Leu	165	170	175
Leu	Ser	Glu	Ala	Asp	Val	Arg	Ala	Leu	Gly	Gly	Leu	Ala	Cys	Asp	Leu	180	185	190
Pro	Gly	Arg	Phe	Val	Ala	Glu	Ser	Ala	Glu	Val	Leu	Leu	Pro	Arg	Leu	195	200	205
Val	Ser	Cys	Pro	Gly	Pro	Leu	Asp	Gln	Asp	Gln	Gln	Glu	Ala	Ala	Arg	210	215	220
Ala	Ala	Leu	Gln	Gly	Gly	Gly	Pro	Pro	Tyr	Gly	Pro	Pro	Ser	Thr	Trp	225	230	235
Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu	Gly	245	250	255
Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp	Arg	260	265	270
Gln	Arg	Ser	Ser	Arg	Asp	Pro	Ser	Trp	Arg	Gln	Pro	Glu	Arg	Thr	Ile	275	280	285
Leu	Arg	Pro	Arg	Phe	Arg	Arg	Glu	Val	Glu	Lys	Thr	Ala	Cys	Pro	Ser	290	295	300
Gly	Lys	Lys	Ala	Arg	Glu	Ile	Asp	Glu	Ser	Leu	Ile	Phe	Tyr	Lys	Lys	305	310	315
Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu	Leu	Ala	Thr	Gln	Met	325	330	335
Asp	Arg	Val	Asn	Ala	Ile	Pro	Phe	Thr	Tyr	Glu	Gln	Leu	Asp	Val	Leu	340	345	350
Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser	Val	355	360	365
Ile	Gln	His	Leu	Gly	Tyr	Leu	Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp	Ile	370	375	380
Arg	Lys	Trp	Asn	Val	Thr	Ser	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu	Glu	385	390	395
Val	Asn	Lys	Gly	His	Glu	Met	Ser	Pro	Gln	Ala	Pro	Arg	Arg	Pro	Leu	405	410	415
Pro	Gln	Val	Ala	Thr	Leu	Ile	Asp	Arg	Phe	Val	Lys	Gly	Arg	Gly	Gln	420	425	430
Leu	Asp	Lys	Asp	Thr	Leu	Asp	Thr	Leu	Thr	Ala	Phe	Tyr	Pro	Gly	Tyr	435	440	445
Leu	Cys	Ser	Leu	Ser	Pro	Glu	Glu	Leu	Ser	Ser	Val	Pro	Pro	Ser	Ser	450	455	460
Ile	Trp	Ala	Val	Arg	Pro	Gln	Asp	Leu	Asp	Thr	Cys	Asp	Pro	Arg	Gln	465	470	475
Leu	Asp	Val	Leu	Tyr	Pro	Lys	Ala	Arg	Leu	Ala	Phe	Gln	Asn	Met	Asn	485	490	495
Gly	Ser	Glu	Tyr	Phe	Val	Lys	Ile	Gln	Ser	Phe	Leu	Gly	Gly	Ala	Pro	500	505	510
Thr	Glu	Asp	Leu	Lys	Ala	Leu	Ser	Gln	Gln	Asn	Val	Ser	Met	Asp	Leu	515	520	525
Ala	Thr	Phe	Met	Lys	Leu	Arg	Thr	Asp	Ala	Val	Leu	Pro	Leu	Thr	Val	530	535	540
Ala	Glu	Val	Gln	Lys	Leu	Leu	Gly	Pro	His	Val	Glu	Gly	Leu	Lys	Ala			

545		550		555		560									
Glu	Glu	Arg	His	Arg	Pro	Val	Arg	Asp	Trp	Ile	Leu	Arg	Gln	Arg	Gln
			565						570					575	
Asp	Asp	Leu	Asp	Thr	Leu	Gly	Leu	Gly	Leu	Gln	Gly	Gly	Ile	Pro	Asn
		580						585					590		
Gly	Tyr	Leu	Val	Leu	Asp	Leu	Ser	Val	Gln	Gly	Gly	Arg	Gly	Gly	Gln
		595					600					605			
Ala	Arg	Ala	Gly	Gly	Arg	Ala	Gly	Gly	Val	Glu	Val	Gly	Ala	Leu	Ser
	610					615					620				
His	Pro	Ser	Leu	Cys	Arg	Gly	Pro	Leu	Gly	Asp	Ala	Leu	Pro	Pro	Arg
625				630						635					640
Thr	Trp	Thr	Cys	Ser	His	Arg	Pro	Gly	Thr	Ala	Pro	Ser	Leu	His	Pro
			645						650					655	
Gly	Leu	Arg	Ala	Pro	Leu	Pro	Cys	Trp	Pro	Gln	Pro	Cys	Trp	Gly	Ser
		660						665					670		
Pro	Pro	Gly	Gln	Glu	Gln	Ala	Arg	Val	Ile	Pro	Val	Pro	Pro	Gln	Glu
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Asn	Ser	Arg	Ser	Val	Asn	Gly	Asn	Met	Pro	Pro	Ala	Asp	Thr		
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<210> 145

<211> 2135

<212> DNA

<213> Homo sapiens

<400> 145

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<210> 146

<211> 630

<212> PRT

<213> Homo sapiens

<400> 146

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Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
  20          25          30
Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
  35          40          45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
  50          55          60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
  65          70          75          80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
  85          90          95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
  100          105          110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
  115          120          125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
  130          135          140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
  145          150          155          160
Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
  165          170          175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
  180          185          190
Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
  195          200          205
Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
  210          215          220
Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
  225          230          235          240
Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
  245          250          255
Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
  260          265          270
Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
  275          280          285
Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
  290          295          300
Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
  305          310          315          320
Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
  325          330          335
Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
  340          345          350
Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
  355          360          365
Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
  370          375          380

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Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
 385 390 395 400
 Val Asn Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Arg Pro Leu
 405 410 415
 Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln
 420 425 430
 Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr
 435 440 445
 Leu Cys Ser Leu Ser Pro Glu Leu Ser Ser Val Pro Pro Ser Ser
 450 455 460
 Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln
 465 470 475 480
 Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn
 485 490 495
 Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro
 500 505 510
 Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu
 515 520 525
 Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val
 530 535 540
 Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala
 545 550 555 560
 Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln
 565 570 575
 Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn
 580 585 590
 Gly Tyr Leu Val Leu Asp Leu Ser Val Gln Glu Ala Leu Ser Gly Thr
 595 600 605
 Pro Cys Leu Leu Gly Pro Gly Pro Val Leu Thr Val Leu Ala Leu Leu
 610 615 620
 Leu Ala Ser Thr Leu Ala
 625 630

<210> 147
 <211> 2105
 <212> DNA
 <213> Homo sapiens

<400> 147
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 tctgtgtgga ccccgccct cggcagcctc ctgttctctgc tcttcagcct cggatgggtg 180
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 aagaatgtca agctctcaac agagcagctg cgctgtcttg ctcaccggct ctctgagccc 420
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<210> 148

<211> 620

<212> PRT

<213> Homo sapiens

<400> 148

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20 25 30
Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
35 40 45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
50 55 60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65 70 75 80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
85 90 95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
100 105 110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
115 120 125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
130 135 140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145 150 155 160
Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
165 170 175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
180 185 190
Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
195 200 205
Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
210 215 220
Ala Ala Leu Gln Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225 230 235 240
Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
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Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
260 265 270
Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile

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275	280	285
Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser		
290	295	300
Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys		
305	310	315
Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met		
325	330	335
Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu		
340	345	350
Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val		
355	360	365
Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile		
370	375	380
Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu		
385	390	395
Val Asn Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Arg Pro Leu		
405	410	415
Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln		
420	425	430
Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr		
435	440	445
Leu Cys Ser Leu Ser Pro Glu Leu Ser Ser Val Pro Pro Ser Ser		
450	455	460
Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln		
465	470	475
Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn		
485	490	495
Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro		
500	505	510
Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu		
515	520	525
Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val		
530	535	540
Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala		
545	550	555
Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln		
565	570	575
Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn		
580	585	590
Gly Tyr Leu Val Leu Asp Leu Ser Val Gln Gly Pro Gly Pro Val Leu		
595	600	605
Thr Val Leu Ala Leu Leu Leu Ala Ser Thr Leu Ala		
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<210> 149

<211> 2193

<212> DNA

<213> Homo sapiens

<400> 149

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cccaggagacc tggacgccct cccattggac ctgctgctat tcctcaaccc agatgcgttc 480

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<210> 150

<211> 694

<212> PRT

<213> Homo sapiens

<400> 150

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Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
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Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
20          25          30
Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
35          40          45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
50          55          60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65          70          75          80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
85          90          95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
100         105         110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
115         120         125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
130         135         140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145         150         155         160
Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
165         170         175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu

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Trp Pro Gln Pro Cys Trp Gly Ser Pro Pro Gly Gln Glu Gln Ala Arg
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 Val Ile Pro Val Pro Pro Gln Glu Asn Ser Arg Ser Val Asn Gly Asn
 675 680 685
 Met Pro Pro Ala Asp Thr
 690

<210> 151

<211> 2081

<212> DNA

<213> Homo sapiens

<400> 151

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tgccccctgc agacacgtaa aaaaaaaaaa aaaaaaaaaa a 2081

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<210> 152

<211> 612

<212> PRT

<213> Homo sapiens

<400> 152

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Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser
 500 505 510
 Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr
 515 520 525
 Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly
 530 535 540
 Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg
 545 550 555 560
 Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu
 565 570 575
 Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser
 580 585 590
 Val Gln Gly Pro Gly Pro Val Leu Thr Val Leu Ala Leu Leu Leu Ala
 595 600 605
 Ser Thr Leu Ala
 610

<210> 153

<211> 2111

<212> DNA

<213> Homo sapiens

<400> 153

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agccctgctg gggatccccg cctggccagg agcaggcacg ggtgatcccc gtccaccccc 2040
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aaaaaaaaa a

2111

<210> 154

<211> 622

<212> PRT

<213> Homo sapiens

<400> 154

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Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
          20           25           30
Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
          35           40           45
Asp Gly Val Leu Ala Asn Pro Asn Ile Ser Ser Leu Ser Pro Arg
          50           55           60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65           70           75           80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
          85           90           95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
          100          105          110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
          115          120          125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
          130          135          140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145          150          155          160
Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
          165          170          175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
          180          185          190
Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
          195          200          205
Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Ala Ala Arg
          210          215          220
Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225          230          235          240
Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
          245          250          255
Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
          260          265          270
Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
          275          280          285
Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
          290          295          300
Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
305          310          315          320
Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
          325          330          335
Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
          340          345          350
Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
          355          360          365
Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
          370          375          380
Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
385          390          395          400
Val Asn Lys Gly His Glu Met Ser Pro Gln Val Ala Thr Leu Ile Asp

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	405		410		415
Arg Phe Val Lys Gly Arg Gly Gln Leu Asp Lys Asp Thr Leu Asp Thr					
	420		425		430
Leu Thr Ala Phe Tyr Pro Gly Tyr Leu Cys Ser Leu Ser Pro Glu Glu					
	435		440		445
Leu Ser Ser Val Pro Pro Ser Ser Ile Trp Ala Val Arg Pro Gln Asp					
	450		455		460
Leu Asp Thr Cys Asp Pro Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala					
	465		470		475
Arg Leu Ala Phe Gln Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile					
	485		490		495
Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser					
	500		505		510
Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr					
	515		520		525
Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly					
	530		535		540
Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg					
	545		550		555
Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu					
	565		570		575
Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser					
	580		585		590
Val Gln Glu Ala Leu Ser Gly Thr Pro Cys Leu Leu Gly Pro Gly Pro					
	595		600		605
Val Leu Thr Val Leu Ala Leu Leu Leu Ala Ser Thr Leu Ala					
	610		615		620

<210> 155

<211> 1721

<212> DNA

<213> Homo sapiens

<400> 155

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agaagttcag tgcccagctc tactgagaag aatgtgtgta gtatgaccag cagcgtactc 240
tccagccaca gccccgggtc aggtctctcc accactcagg gacaggatgt cactctggcc 300
ccggccacgg aaccagcttc aggttcagct gccacctggg gacaggatgt cacctcggtc 360
ccagtcacca ggccagccct gggctccacc accccgccag cccacgatgt cacctcagcc 420
ccggacaaca agccagcccc gggctccacc gcccccccag cccacgggtg cacctcggcc 480
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ccggacaaca ggcccgccct ggcgtccacc gccctccag tcacaaatgt cacctcggcc 720
tcaggctctg catcaggctc agcttctact ctggtgcaca acggcacctc tgccagggtc 780
accacaaccc cagccagcaa gagcactcca ttctcaattc ccagccacca ctctgatact 840
cctaccaccc ttgccagcca tagcaccag actgatgcca gtagcactca ccatagcacg 900
gtacctctc tcacctctc caatcacagc acttctcccc agttgtctac tggggtctct 960
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aaacaagggg gttttctggg cctctccaat attaagttca ggccaggatc tgtggtggtg 1140
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aatcagtata aaacggaagc agcctctcga tataacctga cgatctcaga cgtcagcgtg 1260
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gcgctgctgg tgctggtctg tgttctggtt gcgctggcca ttgtctatct cattgccttg 1380
gctgtctgtc agtgccgcog aaagaactac gggcagctgg acatctttcc agcccgggat 1440

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acctaccatc ctatgagcga gtacccccacc taccacaccc atggggcgcta tgtgccccct 1500
agcagtaccg atcgtagccc ctatgagaag gtttctgcag gtaatgggtgg cagcagcctc 1560
tcttacacaa acccagcagt ggcagccact tctgccaact tgtaggggca cgtcgccctc 1620
tgagctgagt ggccagccag tgccattcca ctccaactcag ggctctctgg gccagtcctc 1680
ctggggagccc ccaccacaac acttcccagg catggaattc c 1721

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<210> 156

<211> 515

<212> PRT

<213> Homo sapiens

<400> 156

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Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Leu Thr
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Val Leu Thr Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly
20      25      30
Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser
35      40      45
Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His
50      55      60
Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu
65      70      75      80
Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln
85      90      95
Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr
100     105     110
Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro
115     120     125
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
130     135     140
Arg Pro Pro Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
145     150     155     160
Ala Pro Asp Thr Arg Pro Pro Pro Gly Ser Thr Ala Pro Ala Ala His
165     170     175
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
180     185     190
Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala Leu
195     200     205
Ala Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly Ser
210     215     220
Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala Arg
225     230     235     240
Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro Ser
245     250     255
His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys Thr
260     265     270
Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser Ser
275     280     285
Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe Phe
290     295     300
Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu Asp
305     310     315     320
Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met
325     330     335
Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile
340     345     350
Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe Arg
355     360     365
Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr

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370	375	380
Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser		
385	390	395
Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val		400
	405	410
Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala		415
	420	425
Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg		430
	435	440
Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His		445
	450	455
Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro		460
465	470	475
Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn		480
	485	490
Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser		495
	500	505
Ala Asn Leu		510
	515	

<210> 157

<211> 4139

<212> DNA

<213> Homo sapiens

<400> 157

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agtgccttaca	gttggttacag	gttctgggtca	tgcaagctct	accccagggtg	gagaaaaagga	180
gacttcgggt	acccagagaa	gttcagtgcc	cagctctact	gagaagaatg	ctgtgagtat	240
gaccagcagc	gtactctcca	gccacagccc	cggttcaggc	tcctccacca	ctcagggaca	300
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ggatgtcacc	tcggtcccag	tcaccaggcc	agccctgggc	tccaccaccc	cgccagccca	420
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cggtgtcacc	tcggccccgg	acaccaggcc	ggccccgggc	tccaccgccc	ccccagccca	540
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cggtgtcacc	tcggccccgg	acaccaggcc	ggccccgggc	tccaccgccc	ccccagccca	960
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cggtgtcacc	tcggccccgg	acaccaggcc	ggccccgggc	tccaccgccc	ccccagccca	1860
cggtgtcacc	tcggccccgg	acaccaggcc	ggccccgggc	tccaccgccc	ccccagccca	1920

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<210> 158

<211> 1255

<212> PRT

<213> Homo sapiens

<400> 158

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Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr
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Val Leu Thr Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly
20      25      30
Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser
35      40      45
Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His
50      55      60
Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu
65      70      75      80
Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln
85      90      95
Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr
100     105     110
Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro

```


Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro
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Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr
	610					615					620				
Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser
625					630					635					640
Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His
				645					650					655	
Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala
			660				665						670		
Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro
		675					680					685			
Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr
	690					695					700				
Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser
705					710					715					720
Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His
				725					730					735	
Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala
			740				745					750			
Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro
		755					760					765			
Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr
	770					775					780				
Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser
785					790					795					800
Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His
				805					810					815	
Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala
			820				825					830			
Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro
		835					840					845			
Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr
	850					855					860				
Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser
865					870					875					880
Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His
				885					890					895	
Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala
			900				905					910			
Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro
		915					920					925			
Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Asn
	930					935					940				
Arg	Pro	Ala	Leu	Gly	Ser	Thr	Ala	Pro	Pro	Val	His	Asn	Val	Thr	Ser
945					950					955					960
Ala	Ser	Gly	Ser	Ala	Ser	Gly	Ser	Ala	Ser	Thr	Leu	Val	His	Asn	Gly
				965					970					975	
Thr	Ser	Ala	Arg	Ala	Thr	Thr	Thr	Pro	Ala	Ser	Lys	Ser	Thr	Pro	Phe
			980					985					990		
Ser	Ile	Pro	Ser	His	His	Ser	Asp	Thr	Pro	Thr	Thr	Leu	Ala	Ser	His
	995						1000					1005			
Ser	Thr	Lys	Thr	Asp	Ala	Ser	Ser	Thr	His	His	Ser	Ser	Val	Pro	Pro
	1010					1015					1020				
Leu	Thr	Ser	Ser	Asn	His	Ser	Thr	Ser	Pro	Gln	Leu	Ser	Thr	Gly	Val
1025					1030					1035					1040
Ser	Phe	Phe	Phe	Leu	Ser	Phe	His	Ile	Ser	Asn	Leu	Gln	Phe	Asn	Ser
				1045					1050					1055	
Ser	Leu	Glu	Asp	Pro	Ser	Thr	Asp	Tyr	Tyr	Gln	Glu	Leu	Gln	Arg	Asp

1060	1065	1070
Ile Ser Glu Met Phe Leu Gln	Ile Tyr Lys Gln Gly Gly Phe Leu Gly	
1075	1080	1085
Leu Ser Asn Ile Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu Thr		
1090	1095	1100
Leu Ala Phe Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln		
1105	1110	1115
Phe Asn Gln Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile		
1125	1130	1135
Ser Asp Val Ser Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser		
1140	1145	1150
Gly Ala Gly Val Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys		
1155	1160	1165
Val Leu Val Ala Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys		
1170	1175	1180
Gln Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg		
1185	1190	1195
Asp Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly		
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<212> DNA

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<400> 159

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<212> PRT

<213> Homo sapiens

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Ile Gly Thr Asp Leu Asp Ala Val Arg Thr Pro Glu Pro Leu Glu Glu
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<210> 164

<211> 1938

<212> PRT

<213> Homo sapiens

<400> 164

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Lys Arg Leu Val Trp Val Pro Ser Glu Lys Gln Gly Phe Glu Ala Ala
35     40     45
Ser Ile Lys Glu Glu Lys Gly Asp Glu Val Val Val Glu Leu Val Glu
50     55     60
Asn Gly Lys Lys Val Thr Val Gly Lys Asp Asp Ile Gln Lys Met Asn
65     70     75     80
Pro Pro Lys Phe Ser Lys Val Glu Asp Met Ala Glu Leu Thr Cys Leu
85     90     95
Asn Glu Ala Ser Val Leu His Asn Leu Arg Glu Arg Tyr Phe Ser Gly
100    105    110
Leu Ile Tyr Thr Tyr Ser Gly Leu Phe Cys Val Val Val Asn Pro Tyr
115    120    125
Lys His Leu Pro Ile Tyr Ser Glu Lys Ile Val Asp Met Tyr Lys Gly
130    135    140
Lys Lys Arg His Glu Met Pro Pro His Ile Tyr Ala Ile Ala Asp Thr
145    150    155    160
Ala Tyr Arg Ser Met Leu Gln Asp Arg Glu Asp Gln Ser Ile Leu Cys
165    170    175
Thr Gly Glu Ser Gly Ala Gly Lys Thr Glu Asn Thr Lys Lys Val Ile
180    185    190
Gln Tyr Leu Ala Val Val Ala Ser Ser His Lys Gly Lys Lys Asp Thr
195    200    205
Ser Ile Thr Gly Glu Leu Glu Lys Gln Leu Leu Gln Ala Asn Pro Ile

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	245	250
Val Gly Ala Asn Ile Glu Thr Tyr Leu Leu Glu Lys Ser Arg Ala Ile		255
	260	265
Arg Gln Ala Arg Asp Glu Arg Thr Phe His Ile Phe Tyr Tyr Met Ile		270
	275	280
Ala Gly Ala Lys Glu Lys Met Arg Ser Asp Leu Leu Leu Glu Gly Phe		285
	290	295
Asn Asn Tyr Thr Phe Leu Ser Asn Gly Phe Val Pro Ile Pro Ala Ala		300
305	310	315
Gln Asp Asp Glu Met Phe Gln Glu Thr Val Glu Ala Met Ala Ile Met		320
	325	330
Gly Phe Ser Glu Glu Glu Gln Leu Ser Ile Leu Lys Val Val Ser Ser		335
	340	345
Val Leu Gln Leu Gly Asn Ile Val Phe Lys Lys Glu Arg Asn Thr Asp		350
	355	360
Gln Ala Ser Met Pro Asp Asn Thr Ala Ala Gln Lys Val Cys His Leu		365
	370	375
Met Gly Ile Asn Val Thr Asp Phe Thr Arg Ser Ile Leu Thr Pro Arg		380
385	390	395
Ile Lys Val Gly Arg Asp Val Val Gln Lys Ala Gln Thr Lys Glu Gln		400
	405	410
Ala Asp Phe Ala Val Glu Ala Leu Ala Lys Ala Thr Tyr Glu Arg Leu		415
	420	425
Phe Arg Trp Ile Leu Thr Arg Val Asn Lys Ala Leu Asp Lys Thr His		430
	435	440
Arg Gln Gly Ala Ser Phe Leu Gly Ile Leu Asp Ile Ala Gly Phe Glu		445
	450	455
Ile Phe Glu Val Asn Ser Phe Glu Gln Leu Cys Ile Asn Tyr Thr Asn		460
465	470	475
Glu Lys Leu Gln Gln Leu Phe Asn His Thr Met Phe Ile Leu Glu Gln		480
	485	490
Glu Glu Tyr Gln Arg Glu Gly Ile Glu Trp Asn Phe Ile Asp Phe Gly		495
	500	505
Leu Asp Leu Gln Pro Cys Ile Glu Leu Ile Glu Arg Pro Asn Asn Pro		510
	515	520
Pro Gly Val Leu Ala Leu Leu Asp Glu Glu Cys Trp Phe Pro Lys Ala		525
	530	535
Thr Asp Lys Ser Phe Val Glu Lys Leu Cys Thr Glu Gln Gly Ser His		540
545	550	555
Pro Lys Phe Gln Lys Pro Lys Gln Leu Lys Asp Lys Thr Glu Phe Ser		560
	565	570
Ile Ile His Tyr Ala Gly Lys Val Asp Tyr Asn Ala Ser Ala Trp Leu		575
	580	585
Thr Lys Asn Met Asp Pro Leu Asn Asp Asn Val Thr Ser Leu Leu Asn		590
	595	600
Ala Ser Ser Asp Lys Phe Val Ala Asp Leu Trp Lys Asp Val Asp Arg		605
	610	615
Ile Val Gly Leu Asp Gln Met Ala Lys Met Thr Glu Ser Ser Leu Pro		620
625	630	635
Ser Ala Ser Lys Thr Lys Lys Gly Met Phe Arg Thr Val Gly Gln Leu		640
	645	650
Tyr Lys Glu Gln Leu Gly Lys Leu Met Thr Thr Leu Arg Asn Thr Thr		655
	660	665
Pro Asn Phe Val Arg Cys Ile Ile Pro Asn His Glu Lys Arg Ser Gly		670
	675	680
		685

Lys Leu Asp Ala Phe Leu Val Leu Glu Gln Leu Arg Cys Asn Gly Val
 690 695 700
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 705 710 715 720
 Phe Gln Glu Phe Arg Gln Arg Tyr Glu Ile Leu Ala Ala Asn Ala Ile
 725 730 735
 Pro Lys Gly Phe Met Asp Gly Lys Gln Ala Cys Ile Leu Met Ile Lys
 740 745 750
 Ala Leu Glu Leu Asp Pro Asn Leu Tyr Arg Ile Gly Gln Ser Lys Ile
 755 760 765
 Phe Phe Arg Thr Gly Val Leu Ala His Leu Glu Glu Glu Arg Asp Leu
 770 775 780
 Lys Ile Thr Asp Val Ile Met Ala Phe Gln Ala Met Cys Arg Gly Tyr
 785 790 795 800
 Leu Ala Arg Lys Ala Phe Ala Lys Arg Gln Gln Gln Leu Thr Ala Met
 805 810 815
 Lys Val Ile Gln Arg Asn Cys Ala Ala Tyr Leu Lys Leu Arg Asn Trp
 820 825 830
 Gln Trp Trp Arg Leu Phe Thr Lys Val Lys Pro Leu Leu Gln Val Thr
 835 840 845
 Arg Gln Glu Glu Glu Met Gln Ala Lys Glu Asp Glu Leu Gln Lys Thr
 850 855 860
 Lys Glu Arg Gln Gln Lys Ala Glu Asn Glu Leu Lys Glu Leu Glu Gln
 865 870 875 880
 Lys His Ser Gln Leu Thr Glu Glu Lys Asn Leu Leu Gln Glu Gln Leu
 885 890 895
 Gln Ala Glu Thr Glu Leu Tyr Ala Glu Ala Glu Glu Met Arg Val Arg
 900 905 910
 Leu Ala Ala Lys Lys Gln Glu Leu Glu Glu Ile Leu His Glu Met Glu
 915 920 925
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 930 935 940
 Arg Lys Lys Met Ala Gln Gln Met Leu Asp Leu Glu Glu Gln Leu Glu
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 Glu Glu Glu Ala Ala Arg Gln Lys Leu Gln Leu Glu Lys Val Thr Ala
 965 970 975
 Glu Ala Lys Ile Lys Lys Leu Glu Asp Glu Ile Leu Val Met Asp Asp
 980 985 990
 Gln Asn Asn Lys Leu Ser Lys Glu Arg Lys Leu Leu Glu Glu Arg Ile
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 Ser Asp Leu Thr Thr Asn Leu Ala Glu Glu Glu Glu Lys Ala Lys Asn
 1010 1015 1020
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 1075 1080 1085
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 1090 1095 1100
 Gln Lys Asn Asn Ala Leu Lys Lys Ile Arg Glu Leu Glu Gly His Ile
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 Ser Asp Leu Gln Glu Asp Leu Asp Ser Glu Arg Ala Ala Arg Asn Lys
 1125 1130 1135
 Ala Glu Lys Gln Lys Arg Asp Leu Gly Glu Glu Leu Glu Ala Leu Lys
 1140 1145 1150
 Thr Glu Leu Glu Asp Thr Leu Asp Ser Thr Ala Thr Gln Gln Glu Leu

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Asn Ala Asp Leu Ala Gly Glu Leu Arg Val Leu Gly Gln Ala Lys Gln		
1235	1240	1245
Glu Val Glu His Lys Lys Lys Lys Leu Glu Ala Gln Val Gln Glu Leu		
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Gln Ser Lys Cys Ser Asp Gly Glu Arg Ala Arg Ala Glu Leu Asn Asp		
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Lys Val His Lys Leu Gln Asn Glu Val Glu Ser Val Thr Gly Met Leu		
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Asn Glu Ala Glu Gly Lys Ala Ile Lys Leu Ala Lys Asp Val Ala Ser		
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Leu Ser Ser Gln Leu Gln Asp Thr Gln Glu Leu Leu Gln Glu Glu Thr		
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Arg Gln Lys Leu Asn Val Ser Thr Lys Leu Arg Gln Leu Glu Glu Glu		
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Arg Asn Ser Leu Gln Asp Gln Leu Asp Glu Glu Met Glu Ala Lys Gln		
1345	1350	1355
Asn Leu Glu Arg His Ile Ser Thr Leu Asn Ile Gln Leu Ser Asp Ser		
1365	1370	1375
Lys Lys Lys Leu Gln Asp Phe Ala Ser Thr Val Glu Ala Leu Glu Glu		
1380	1385	1390
Gly Lys Lys Arg Phe Gln Lys Glu Ile Glu Asn Leu Thr Gln Gln Tyr		
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Leu Gln Gln Glu Leu Asp Asp Leu Val Val Asp Leu Asp Asn Gln Arg		
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Gln Leu Val Ser Asn Leu Glu Lys Lys Gln Arg Lys Phe Asp Gln Leu		
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Leu Ala Glu Glu Lys Asn Ile Ser Ser Lys Tyr Ala Asp Glu Arg Asp		
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1475	1480	1485
Ala Arg Ala Leu Glu Glu Ala Leu Glu Ala Lys Glu Glu Leu Glu Arg		
1490	1495	1500
Thr Asn Lys Met Leu Lys Ala Glu Met Glu Asp Leu Val Ser Ser Lys		
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Asp Asp Val Gly Lys Asn Val His Glu Leu Glu Lys Ser Lys Arg Ala		
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Leu Glu Thr Gln Met Glu Glu Met Lys Thr Gln Leu Glu Glu Leu Glu		
1540	1545	1550
Asp Glu Leu Gln Ala Thr Glu Asp Ala Lys Leu Arg Leu Glu Val Asn		
1555	1560	1565
Met Gln Ala Leu Lys Gly Gln Phe Glu Arg Asp Leu Gln Ala Arg Asp		
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Glu Gln Asn Glu Glu Lys Arg Arg Gln Leu Gln Arg Gln Leu His Glu		
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Tyr Glu Thr Glu Leu Glu Asp Glu Arg Lys Gln Arg Ala Leu Ala Ala		
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Ala Ala Lys Lys Lys Leu Glu Gly Asp Leu Lys Asp Leu Glu Leu Gln		
1620	1625	1630

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 1665 1670 1675 1680
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 Thr Lys Ser Leu Lys Gln Lys Asp Lys Lys Leu Lys Glu Ile Leu Leu
 1845 1850 1855
 Gln Val Glu Asp Glu Arg Lys Met Ala Glu Gln Tyr Lys Glu Gln Ala
 1860 1865 1870
 Glu Lys Gly Asn Ala Arg Val Lys Gln Leu Lys Arg Gln Leu Glu Glu
 1875 1880 1885
 Ala Glu Glu Glu Ser Gln Arg Ile Asn Ala Asn Arg Arg Lys Leu Gln
 1890 1895 1900
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 1905 1910 1915 1920
 Val Asn Ala Leu Lys Ser Lys Leu Arg Gly Pro Pro Pro Gln Glu Thr
 1925 1930 1935
 Ser Gln

<210> 165

<211> 958

<212> DNA

<213> Homo sapiens

<400> 165

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<210> 166

<211> 234

<212> PRT

<213> Homo sapiens

<400> 166

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Val	Ser	Ala	Cys	Asp	Thr	Glu	Asp	Thr	Val	Gly	His	Leu	Gly	Pro	Trp
		35					40					45			
Arg	Asp	Lys	Asp	Pro	Ala	Leu	Trp	Cys	Gln	Leu	Cys	Leu	Ser	Ser	Gln
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His	Gln	Ala	Ile	Glu	Arg	Phe	Tyr	Asp	Lys	Met	Gln	Asn	Ala	Glu	Ser
65					70				75						80
Gly	Arg	Gly	Gln	Val	Met	Ser	Ser	Leu	Ala	Glu	Leu	Glu	Asp	Asp	Phe
				85					90					95	
Lys	Glu	Gly	Tyr	Leu	Glu	Thr	Val	Ala	Ala	Tyr	Tyr	Glu	Glu	Gln	His
			100					105					110		
Pro	Glu	Leu	Thr	Pro	Leu	Leu	Glu	Lys	Glu	Arg	Asp	Gly	Leu	Arg	Cys
		115					120					125			
Arg	Gly	Asn	Arg	Ser	Pro	Val	Pro	Asp	Val	Glu	Asp	Pro	Ala	Thr	Glu
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Glu	Pro	Gly	Glu	Ser	Phe	Cys	Asx	Lys	Val	Met	Arg	Trp	Phe	Gln	Ala
145					150				155						160
Met	Leu	Gln	Arg	Leu	Gln	Thr	Trp	Trp	His	Gly	Val	Leu	Ala	Trp	Val
				165					170					175	
Lys	Glu	Lys	Val	Val	Ala	Leu	Val	His	Ala	Val	Gln	Ala	Leu	Trp	Lys
			180					185					190		
Gln	Phe	Gln	Ser	Phe	Cys	Cys	Ser	Leu	Ser	Glu	Leu	Phe	Met	Ser	Ser
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Phe	Gln	Ser	Tyr	Gly	Ala	Pro	Arg	Gly	Asp	Lys	Glu	Glu	Leu	Thr	Pro
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Gln	Lys	Cys	Ser	Glu	Pro	Gln	Ser	Ser	Lys						
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<210> 167

<211> 958

<212> DNA

<213> Homo sapiens

<400> 167

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 ctgtgggaca cctgggaccc tggagggaca aggatccggc cctttggtgc caactctgcc 240
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 ccgcaaccga ggagcctggg gagagctttt gtgacaaggt catgagatgg ttccaggcca 540

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<210> 168

<211> 234

<212> PRT

<213> Homo sapiens

<400> 168

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Val Ser Ala Cys Asp Thr Glu Asp Thr Val Gly His Leu Gly Pro Trp
35     40     45
Arg Asp Lys Asp Pro Ala Leu Trp Cys Gln Leu Cys Leu Ser Ser Gln
50     55     60
His Gln Ala Ile Glu Arg Phe Tyr Asp Lys Met Gln Asn Ala Glu Ser
65     70     75     80
Gly Arg Gly Gln Val Met Ser Ser Leu Ala Glu Leu Glu Asp Asp Phe
85     90     95
Lys Glu Gly Tyr Leu Glu Thr Val Ala Ala Tyr Tyr Glu Glu Gln His
100    105    110
Pro Glu Leu Thr Pro Leu Leu Glu Lys Glu Arg Asp Gly Leu Arg Cys
115    120    125
Arg Gly Asn Arg Ser Pro Val Pro Asp Val Glu Asp Pro Ala Thr Glu
130    135    140
Glu Pro Gly Glu Ser Phe Cys Asp Lys Val Met Arg Trp Phe Gln Ala
145    150    155    160
Met Leu Gln Arg Leu Gln Thr Trp Trp His Gly Val Leu Ala Trp Val
165    170    175
Lys Glu Lys Val Val Ala Leu Val His Ala Val Gln Ala Leu Trp Lys
180    185    190
Gln Phe Gln Ser Phe Cys Cys Ser Leu Ser Glu Leu Phe Met Ser Ser
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<210> 169

<211> 1005

<212> DNA

<213> Homo sapiens

<400> 169

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gggcccggagc tatggcttaa gccgagaggt gcaggagaag atcgagcaga agtatgatgc 120
ggacctggag aacaagctgg tggactggat catcctgcag tgcgcccagg acatagagca 180
cccgccccc ggcaggggcc attttcagaa atgggttaat gacgggacgg tcctgtgcaa 240
gctgataaat agtttatacc caccaggaca agagcccata cccaagatct cagagtcaaa 300
gatggctttt aagcagatgg agcaaatctc ccagttccta aaagctgcgg agacctatgg 360
tgtcagaacc accgacatct ttcagacggt ggatctatgg gaagggaagg acatggcagc 420

```



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tgtgcagagg accctgatgg ctttaggcag cgttgacagtc accaaggatg atggctgcta 480
tcggggagag ccatcctggt ttacacaggaa agcccagcag aatcggagag gcttttccga 540
ggagcagcct cgccagggac agaacgtaat aggcctgcag atgggcagca acaagggagc 600
ctcccaggcg ggcacgacag ggtacgggat gccacggcag atcatgttag gacgcggcat 660
cctgcccctg gtagagagga cgaatgttcc acaccatggg ctctacgaaa aagaaatagt 720
tagtcacctt ctgaccttct cctctttctc aaagccttct gtccctgggt tttgcaagtg 780
ctgcatttcc gccgagaatc cgcgttgctt actgctgcca cctcctgttc atttagaact 840
atgcaaagac tccgcttccg ttttctgag ctccctgggc cccagagtct ctgtttgatt 900
atttatttat ttatttattt atttgccaaa aattctcctc ttcaacttat agaatgcacc 960
taataaagta attaatgtct gtggaaaaaa aaaaaaaaaa aaaaaa 1005

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<210> 170

<211> 282

<212> PRT

<213> Homo sapiens

<400> 170

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Met Ala Asn Arg Gly Pro Ser Tyr Gly Leu Ser Arg Glu Val Gln Glu
  1          5          10          15
Lys Ile Glu Gln Lys Tyr Asp Ala Asp Leu Glu Asn Lys Leu Val Asp
      20          25          30
Trp Ile Ile Leu Gln Cys Ala Glu Asp Ile Glu His Pro Pro Gly
  35          40          45
Arg Ala His Phe Gln Lys Trp Leu Met Asp Gly Thr Val Leu Cys Lys
  50          55          60
Leu Ile Asn Ser Leu Tyr Pro Pro Gly Gln Glu Pro Ile Pro Lys Ile
  65          70          75          80
Ser Glu Ser Lys Met Ala Phe Lys Gln Met Glu Gln Ile Ser Gln Phe
      85          90          95
Leu Lys Ala Ala Glu Thr Tyr Gly Val Arg Thr Thr Asp Ile Phe Gln
      100          105          110
Thr Val Asp Leu Trp Glu Gly Lys Asp Met Ala Ala Val Gln Arg Thr
      115          120          125
Leu Met Ala Leu Gly Ser Val Ala Val Thr Lys Asp Asp Gly Cys Tyr
      130          135          140
Arg Gly Glu Pro Ser Trp Phe His Arg Lys Ala Gln Gln Asn Arg Arg
      145          150          155          160
Gly Phe Ser Glu Glu Gln Leu Arg Gln Gly Gln Asn Val Ile Gly Leu
      165          170          175
Gln Met Gly Ser Asn Lys Gly Ala Ser Gln Ala Gly Met Thr Gly Tyr
      180          185          190
Gly Met Pro Arg Gln Ile Met Leu Gly Arg Gly Ile Leu Pro Leu Val
      195          200          205
Glu Arg Thr Asn Val Pro His His Gly Leu Tyr Glu Lys Glu Ile Val
      210          215          220
Ser His Leu Leu Thr Phe Ser Ser Phe Ser Lys Pro Ser Val Pro Gly
      225          230          235          240
Phe Cys Lys Cys Cys Ile Ser Ala Glu Asn Pro Arg Cys Leu Leu Leu
      245          250          255
Pro Pro Pro Val His Leu Glu Leu Cys Lys Asp Ser Ala Ser Val Phe
      260          265          270
Leu Ser Ser Ser Gly Pro Arg Val Ser Val
      275          280

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<210> 171

<211> 942

<212> DNA

<213> Homo sapiens

<400> 171

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atgagaattg cagtgatttg cttttgcctc ctaggcatca cctgtgccat accagttaaa 60
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gccacatggc taaaccctga cccatctcag aagcagaatc tcctagcccc acagaatgct 180
gtgtcctctg aagaaaccaa tgactttaaa caagagaccc ttccaagtaa gtccaacgaa 240
agccatgacc acatggatga tatggatgat gaagatgatg atgaccatgt ggacagccag 300
gactccattg actcgaacga ctctgatgat gtagatgaca ctgatgattc tcaccagtct 360
gatgagtctc accattctga tgaatctgat gaactgggtc ctgattttcc cacggacctg 420
ccagcaaccg aagttttcac tccagttgtc cccacagtag acacatatga tggccgaggt 480
gatagtgtgg tttatggact gaggtcaaaa tctaagaagt ttgcagacc tgacatccag 540
taccctgatg ctacagacga gcacatcacc tcacacatgg aaagcgagga gttgaatgg 600
gcatacaagg ccatccccgt tgcccaggac ctgaacgcgc cttctgattg ggacagccgt 660
gggaaggaca gttatgaaac gattcagctg gatgaccaga gtgctgaagc ccacagccac 720
aagcagtcca gattatataa gcggaaagct aatgatgaga gcaatgagca ttccgatgtg 780
attgatagtc aggaactttc caaagtcagc cgtgaattcc acagccatga atttcacagc 840
catgaagata tgctggttgt agaccccaaa agtaaggaag aagataaaca cctgaaattt 900
cgtattttctc atgaattaga tagtgcatct tctgaggtca at 942

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<210> 172

<211> 314

<212> PRT

<213> Homo sapiens

<400> 172

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Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
1      5      10      15
Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu
20      25      30
Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro
35      40      45
Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Asn Ala Val Ser Ser Glu
50      55      60
Glu Thr Asn Asp Phe Lys Gln Glu Thr Leu Pro Ser Lys Ser Asn Glu
65      70      75      80
Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp Asp His
85      90      95
Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp Val Asp
100     105     110
Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser Asp Glu
115     120     125
Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala Thr Glu
130     135     140
Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly Arg Gly
145     150     155     160
Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe Arg Arg
165     170     175
Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu His Ile Thr Ser His
180     185     190
Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro Val Ala
195     200     205
Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys Asp Ser
210     215     220
Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Ala His Ser His
225     230     235     240
Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser Asn Glu
245     250     255
His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser Arg Glu
260     265     270

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Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val Val Asp
 275 280 285
 Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile Ser His
 290 295 300
 Glu Leu Asp Ser Ala Ser Ser Glu Val Asn
 305 310

<210> 173
 <211> 1524
 <212> DNA
 <213> Homo sapiens

<400> 173
 gcagagcaca gcatcgctgg gaccagactc gtctcaggcc agttgcagcc ttctcagcca 60
 aacgccgacc aaggaaaact cactaccatg agaattgcag tgatttgctt ttgcctccta 120
 ggcatacact gtgccatacc agttaaacag gctgattctg gaagttctga ggaaaagcag 180
 ctttacaaca aatacccaga tgctgtggcc acatggctaa accctgaccc atctcagaag 240
 cagaatctcc tagccccaca gacccttcca agtaagtcca acgaaagcca tgaccacatg 300
 gatgatatgg atgatgaaga tgatgatgac catgtggaca gccaggactc cattgactcg 360
 aacgactctg atgatgtaga tgacactgat gattctcacc agtctgatga gtctcaccat 420
 tctgatgaat ctgatgaact ggtcactgat tttccacgg acctgccagc aaccgaagtt 480
 ttcactccag ttgtccccac agtagacaca tatgatggcc gaggtgatag tgtggtttat 540
 ggactgaggt caaaatctaa gaagtttcgc agacctgaca tccagtaccc tgatgctaca 600
 gacgaggaca tcacctcaca catggaaagc gaggagtga atggtgcata caaggccatc 660
 cccgttgccc aggacctgaa cgcgcttctt gattgggaca gccgtgggaa ggacagttat 720
 gaaacgagtc agctggatga ccagagtgtt gaaaccaca gccacaagca gtccagatta 780
 tataagcggg aagccaatga tgagagcaat gagcattccg atgtgattga tagtcaggaa 840
 ctttccaaag tcagccgtga attccacagc catgaatttc acagccatga agatatgctg 900
 gttgtagacc ccaaaagtaa ggaagaagat aaacacctga aatttcgtat ttctcatgaa 960
 ttagatagtg catcttctga ggtcaattaa aaggagaaaa aatacaattt ctacttttgc 1020
 atttagtcaa aagaaaaaat gctttatagc aaaatgaaag agaacatgaa atgcttcttt 1080
 ctcagtttat tggttgaatg tgtatctatt tgagtctgga aataactaat gtgtttgata 1140
 attagtttag tttgtggctt catggaaact ccctgtaaac taaaagcttc agggttatgt 1200
 ctatgttcat tctatagaag aaatgcaaac tatcactgta ttttaattat tgttattctc 1260
 tcatgaatag aaatttatgt agaagcaaac aaaatacttt taccactta aaaagagaat 1320
 ataacatttt atgtcactat aatcttttgt tttttaagtt agtgtatatt ttgttgtgat 1380
 tatctttttg tgggtgtgaat aaatctttta tcttgaatgt aataagaatt tgggtggtgtc 1440
 aattgcttat ttgttttccc acggttgtcc agcaattaat aaaacataac cttttttact 1500
 gcctaaaaaa aaaaaaaaaa aaaa 1524

<210> 174
 <211> 300
 <212> PRT
 <213> Homo sapiens

<400> 174
 Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
 1 5 10 15
 Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu
 20 25 30
 Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro
 35 40 45
 Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Thr Leu Pro Ser Lys Ser
 50 55 60
 Asn Glu Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp
 65 70 75 80
 Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp
 85 90 95

Val Asp Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser
 100 105 110
 Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala
 115 120 125
 Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly
 130 135 140
 Arg Gly Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe
 145 150 155 160
 Arg Arg Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu Asp Ile Thr
 165 170 175
 Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro
 180 185 190
 Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys
 195 200 205
 Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Thr His
 210 215 220
 Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser
 225 230 235 240
 Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser
 245 250 255
 Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val
 260 265 270
 Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile
 275 280 285
 Ser His Glu Leu Asp Ser Ala Ser Ser Glu Val Asn
 290 295 300

<210> 175
 <211> 861
 <212> DNA
 <213> Homo sapiens

<400> 175
 atgagaattg cagtgtattg cttttgcctc ctaggcatca cctgtgccat accagttaaa 60
 caggctgatt ctggaagtgc tgaggaaaag cagaatgctg tgtcctctga agaaaccaat 120
 gacttttaaac aagagaccct tccaagtaag tccaacgaaa gccatgacca catggatgat 180
 atggatgatg aagatgatga tgaccatgtg gacagccagg actccattga ctggaacgac 240
 tctgatgatg tagatgacac tgatgattct caccagtctg atgagtctca ccattctgat 300
 gaatctgatg aactgggtcac tgattttccc acggacctgc cagcaaccga agttttcact 360
 ccagttgttc ccacagtaga cacatatgat ggccgaggtg atagtgtggt ttatggactg 420
 aggtcaaaaat ctaagaagtt tcgcagacct gacatccagt accctgatgc tacagacgag 480
 cacatcacct cacacatgga aagcgaggag ttgaatggtg catacaaggc catccccgtt 540
 gcccaggacc tgaacgcgcc ttctgattgg gacagccgtg ggaaggacag ttatgaaacg 600
 agtcagctgg atgaccagag tgctgaagcc cacagccaca agcagtcacg attatataag 660
 cggaaagcta atgatgagag caatgagcat tccgatgtga ttgatagtca ggaactttcc 720
 aaagtcagcc gtgaattcca cagccatgaa ttccacagcc atgaagatat gctggttgta 780
 gaccccaaaa gtaagggaaga agataaacac ctgaaatttc gtattttctca tgaattagat 840
 agtgcacatt ctgagggtcaa t 861

<210> 176
 <211> 287
 <212> PRT
 <213> Homo sapiens

<400> 176
 Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
 1 5 10 15
 Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Asn

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<210> 177
<211> 3213
<212> DNA
<213> Homo sapiens
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<400> 177					
agagactcaa	gatgattccc	tttttaccca	tgttttctct	actattgctg	cttattgtta 60
accctataaa	cgccaacaat	cattatgaca	agatcttggc	tcatagtcgt	atcagggggtc 120
gggaccaagg	cccaaattgc	tgtgcccttc	aacagatttt	gggcacaaaa	aagaaatact 180
tcagcaattg	taaagaactg	tataaaaagt	ccatctgttg	acagaaaaac	actgtttttat 240
atgaattgtt	ccctggttat	atgagaattg	aaggaatgaa	aggctgccca	gcagtttttgc 300
ccattgacca	tgtttatggc	actctgggca	tcgtgggagc	caccacaacg	cagcgctatt 360
ctgacgcctc	aaaactgagg	gaggagatcg	agggaaaggg	atccttctact	tactttgcac 420
cgagtaatga	ggcttgggac	aacttggaat	ctgatatccg	tagaggtttg	gagagcaacg 480
tgaatgttga	attactgaat	gctttacata	gtcacatgat	taataagaga	atgttgacca 540
aggacttaaa	aaatggcatg	attattcctt	caatgtataa	caatttgggg	cttttccatta 600
accattatcc	taatgggggt	gtcactgtta	attgtgctcg	aatcatccat	gggaaccaga 660
ttgcaacaaa	tgggtgtgtc	catgtcattg	accgtgtgct	tacacaaatt	ggtagctcaa 720
ttcaagactt	cattgaagca	gaagatgacc	tttcatcttt	tagagcagct	gccatcacat 780
cggacatatt	ggaggccctt	ggaagagacg	gtcacttcac	actctttgct	ccaccaaatg 840
aggcttttga	gaaacttcca	cgagggtgcc	tagaaaggtt	catgggagac	aaagtggctt 900
ccgaagctct	tatgaagtac	cacatcttaa	atactctcca	gtgttctctg	tctattatgg 960
gaggagcagt	ctttgagacg	cttgaaggaa	atacaattga	gataggatgt	gcaggtgaca 1020
gtataacagt	aaatggaatc	aaaattggta	acaaaaagga	tattgtgaca	aataatggtg 1080

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tgatccattt gattgatcag gtccctaattc ctgattctgc caaacaagtt attgagctgg 1140
ctggaaaaaca gcaaaccacc ttcaacggatc ttgtggccca attaggcttg gcatctgctc 1200
tgaggccaga tggagaatac acttttgctgg cacctgtgaa taatgcattt tctgatgata 1260
ctctcagcat ggttcagcgc ctcccttaaat taattctgca gaatcacata ttgaaagtaa 1320
aagttggcct taatgagctt tacaacgggc aaatactgga aaccatcgga ggcaaacagc 1380
tcagagtctt cgtatatcgt acagctgtct gcattgaaaa ttcattgcatg gagaaagggg 1440
gtaagcaagg gagaaacggg gcgattcaca tattccgcga gatcatcaag ccagcagaga 1500
aatccctcca tgaaaagtta aaacaagata agcgctttag caccttcctc agcctacttg 1560
aagctgcaga cttgaaagag ctccctgacac aacctggaga ctggacatta tttgtgccaa 1620
ccaatgatgc ttttaaggga atgactagtg aagaaaaaga aattctgata cgggacaaaa 1680
atgctcttca aaacatcatt ctttatcacc tgacaccagg agttttcatt ggaaaaggat 1740
ttgaacctgg tgttactaac attttaaaga ccacacaagg aagcaaaatc tttctgaaag 1800
aagtaaataa tacacttctg gtgaatgaat tgaaatcaaa agaattctgac atcatgacaa 1860
caaattggtg aattcatgtt gtagataaac tcctctatcc agcagacaca cctggttgaa 1920
atgatcaact gctggaaata ctttaataaat taatcaaata catccaaatt aagtttgttc 1980
gtggtagcac cttcaaagaa atcccgtga ctgtctatac aactaaaatt ataaccaaag 2040
ttgtggaacc aaaaattaaa gtgattgaag gcagtcttca gcctattatc aaaactgaag 2100
gacccacact aacaaaagtc aaaattgaag gtgaacctga attcagactg attaaagaag 2160
gtgaaacaat aactgaagtg atccatggag agccaattat taaaaaatac accaaaatca 2220
ttgatggagt gcctgtggaa ataactgaaa aagagacacg agaagaacga atcattacag 2280
gtcctgaaat aaaatacact aggatttcta ctggaggtgg agaaacagaa gaaactctga 2340
agaaattggt acaagaagag gtcaccaagg tcaccaaatt cattgaaggt ggtgatggtc 2400
atattattga agatgaagaa attaaaagac tgcttcaggg agacacaccc gtgaggaagt 2460
tgcaagccaa caaaaaagtt caaggttcta gaagacgatt aagggaaggt cgttctcagt 2520
gaaaatccaa aaaccagaaa aaaatgttta tacaacccta agtcaataac ctgaccttag 2580
aaaattgtga gagccaagtt gacttcagga actgaaacat cagcacaaag aagcaatcat 2640
caaataattc tgaacacaaa tttaatatatt ttttttctga atgagaaaaca tgagggaaat 2700
tgtggagtta gcctcctgtg gtaaaggaat tgaagaaaat ataacacctt acaccctttt 2760
tcattcttgac attaaaagtt ctggctaact ttggaatcca ttagagaaaa atccttgtca 2820
ccagattcat tacaattcaa atcgaagagt tgtgaactgt tatcccatg aaaagaccga 2880
gccttgtag tatgttatgg atacataaaa tgcacgcaag ccattatctc tccatgggaa 2940
gctaagttat aaaaataggt gcttgggtgta caaaactttt tatatcaaaa ggctttgcac 3000
atctctatat gagtgggttt actggtaaat tatgttattt tttacaacta attttgtact 3060
ctcagaatgt ttgtcatatg cttcttgcaa tgcataattt ttaatctcaa acgtttcaat 3120
aaaaccattt ttcagatata aagagaatta cttcaaatg agtaattcag aaaaactcaa 3180
gatttaagtt aaaaagtggt ttggacttgg gaa 3213

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<210> 178

<211> 836

<212> PRT

<213> Homo sapiens

<400> 178

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Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu Leu Ile Val
1          5          10          15
Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu Ala His Ser
20          25          30
Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala Leu Gln Gln
35          40          45
Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys Asn Trp Tyr
50          55          60
Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys
65          70          75          80
Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro Ala Val Leu
85          90          95
Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly Ala Thr Thr
100         105         110
Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu Ile Glu Gly
115         120         125

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Lys	Gly	Ser	Phe	Thr	Tyr	Phe	Ala	Pro	Ser	Asn	Glu	Ala	Trp	Asp	Asn	130	135	140
Leu	Asp	Ser	Asp	Ile	Arg	Arg	Gly	Leu	Glu	Ser	Asn	Val	Asn	Val	Glu	145	150	155
Leu	Leu	Asn	Ala	Leu	His	Ser	His	Met	Ile	Asn	Lys	Arg	Met	Leu	Thr	165	170	175
Lys	Asp	Leu	Lys	Asn	Gly	Met	Ile	Ile	Pro	Ser	Met	Tyr	Asn	Asn	Leu	180	185	190
Gly	Leu	Phe	Ile	Asn	His	Tyr	Pro	Asn	Gly	Val	Val	Thr	Val	Asn	Cys	195	200	205
Ala	Arg	Ile	Ile	His	Gly	Asn	Gln	Ile	Ala	Thr	Asn	Gly	Val	Val	His	210	215	220
Val	Ile	Asp	Arg	Val	Leu	Thr	Gln	Ile	Gly	Thr	Ser	Ile	Gln	Asp	Phe	225	230	235
Ile	Glu	Ala	Glu	Asp	Leu	Ser	Ser	Phe	Arg	Ala	Ala	Ala	Ile	Thr		245	250	255
Ser	Asp	Ile	Leu	Glu	Ala	Leu	Gly	Arg	Asp	Gly	His	Phe	Thr	Leu	Phe	260	265	270
Ala	Pro	Thr	Asn	Glu	Ala	Phe	Glu	Lys	Leu	Pro	Arg	Gly	Val	Leu	Glu	275	280	285
Arg	Phe	Met	Gly	Asp	Lys	Val	Ala	Ser	Glu	Ala	Leu	Met	Lys	Tyr	His	290	295	300
Ile	Leu	Asn	Thr	Leu	Gln	Cys	Ser	Glu	Ser	Ile	Met	Gly	Gly	Ala	Val	305	310	315
Phe	Glu	Thr	Leu	Glu	Gly	Asn	Thr	Ile	Glu	Ile	Gly	Cys	Asp	Gly	Asp	325	330	335
Ser	Ile	Thr	Val	Asn	Gly	Ile	Lys	Met	Val	Asn	Lys	Lys	Asp	Ile	Val	340	345	350
Thr	Asn	Asn	Gly	Val	Ile	His	Leu	Ile	Asp	Gln	Val	Leu	Ile	Pro	Asp	355	360	365
Ser	Ala	Lys	Gln	Val	Ile	Glu	Leu	Ala	Gly	Lys	Gln	Gln	Thr	Thr	Phe	370	375	380
Thr	Asp	Leu	Val	Ala	Gln	Leu	Gly	Leu	Ala	Ser	Ala	Leu	Arg	Pro	Asp	385	390	395
Gly	Glu	Tyr	Thr	Leu	Ala	Pro	Val	Asn	Asn	Ala	Phe	Ser	Asp	Asp		405	410	415
Thr	Leu	Ser	Met	Val	Gln	Arg	Leu	Leu	Lys	Leu	Ile	Leu	Gln	Asn	His	420	425	430
Ile	Leu	Lys	Val	Lys	Val	Gly	Leu	Asn	Glu	Leu	Tyr	Asn	Gly	Gln	Ile	435	440	445
Leu	Glu	Thr	Ile	Gly	Gly	Lys	Gln	Leu	Arg	Val	Phe	Val	Tyr	Arg	Thr	450	455	460
Ala	Val	Cys	Ile	Glu	Asn	Ser	Cys	Met	Glu	Lys	Gly	Ser	Lys	Gln	Gly	465	470	475
Arg	Asn	Gly	Ala	Ile	His	Ile	Phe	Arg	Glu	Ile	Ile	Lys	Pro	Ala	Glu	485	490	495
Lys	Ser	Leu	His	Glu	Lys	Leu	Lys	Gln	Asp	Lys	Arg	Phe	Ser	Thr	Phe	500	505	510
Leu	Ser	Leu	Leu	Glu	Ala	Ala	Asp	Leu	Lys	Glu	Leu	Leu	Thr	Gln	Pro	515	520	525
Gly	Asp	Trp	Thr	Leu	Phe	Val	Pro	Thr	Asn	Asp	Ala	Phe	Lys	Gly	Met	530	535	540
Thr	Ser	Glu	Glu	Lys	Glu	Ile	Leu	Ile	Arg	Asp	Lys	Asn	Ala	Leu	Gln	545	550	555
Asn	Ile	Ile	Leu	Tyr	His	Leu	Thr	Pro	Gly	Val	Phe	Ile	Gly	Lys	Gly	565	570	575
Phe	Glu	Pro	Gly	Val	Thr	Asn	Ile	Leu	Lys	Thr	Thr	Gln	Gly	Ser	Lys	580	585	590
Ile	Phe	Leu	Lys	Glu	Val	Asn	Asp	Thr	Leu	Leu	Val	Asn	Glu	Leu	Lys			

595	600	605
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Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile Lys Phe Val		
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Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr Thr Thr Lys		
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Ile Ile Thr Lys Val Val Glu Pro Lys Ile Lys Val Ile Glu Gly Ser		
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Leu Gln Pro Ile Ile Lys Thr Glu Gly Pro Thr Leu Thr Lys Val Lys		
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Arg Ile Ile Thr Gly Pro Glu Ile Lys Tyr Thr Arg Ile Ser Thr Gly		
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Thr Lys Val Thr Lys Phe Ile Glu Gly Gly Asp Gly His Leu Phe Glu		
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<211> 3077

<212> DNA

<213> Homo sapiens

<400> 179

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<210> 180

<211> 779

<212> PRT

<213> Homo sapiens

<400> 180

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Leu Asp Ser Asp Ile Arg Arg Gly Leu Glu Ser Asn Val Asn Val Glu
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<210> 181

<211> 2088

<212> DNA

<213> Homo sapiens

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 <211> 334
 <212> PRT
 <213> Homo sapiens

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 Pro Ala Glu Asp Val Thr Pro Gln Pro Leu Gln Arg Arg Pro Cys Pro
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<210> 184

<211> 431

<212> PRT

<213> Homo sapiens

<400> 184

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20      25      30
Cys Leu Asn Gly Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile
35      40      45
His Trp Cys Asn Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile
50      55      60
Asp Lys Ser Lys Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly
65      70      75      80
Lys Ala Ser Thr Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser
85      90      95

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Ala Thr Val Leu Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu
 100 105 110
 Gln Leu Gly Leu Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg
 115 120 125
 Arg Arg Pro Trp Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln
 130 135 140
 Glu Cys Met Val His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro
 145 150 155 160
 Pro Glu Glu Leu Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg
 165 170 175
 Phe Lys Ile Ile Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp
 180 185 190
 Phe Ala Ala Ile Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val
 195 200 205
 Cys Gly Gly Ser Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His
 210 215 220
 Cys Phe Ile Asp Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly
 225 230 235 240
 Arg Ser Arg Leu Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val
 245 250 255
 Glu Asn Leu Ile Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His
 260 265 270
 His Asn Asp Ile Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys
 275 280 285
 Ala Gln Pro Ser Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr
 290 295 300
 Asn Asp Pro Gln Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys
 305 310 315 320
 Glu Asn Ser Thr Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val
 325 330 335
 Val Lys Leu Ile Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly
 340 345 350
 Ser Glu Val Thr Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys
 355 360 365
 Thr Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu
 370 375 380
 Gln Gly Arg Met Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys
 385 390 395 400
 Ala Leu Lys Asp Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu
 405 410 415
 Pro Trp Ile Arg Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
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<210> 185

<211> 2123

<212> DNA

<213> Homo sapiens

<400> 185

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 gccgggggtcc ccggagttgc agctcccga gctccggcgg cggtccacc ggcgaaagag 180
 atcccggagg tcctagtga cccacgcagc cggcggcgct atgtcgggg ccgctttttg 240
 ggcaagggcg gctttgcaa gtgcttcgag atctcggacg cggacaccaa ggaggtgttc 300
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 atggaaatat ccattcaccg cagcctcgcc caccagcacg tcgtaggatt ccacggcttt 420
 ttcgaggaca acgacttcgt gttcgtggtg ttggagctct gccgccggag gtctctcctg 480
 gagccgcaca agaggaggaa agccctgact gagcctgagg cccgatacta cctacggcaa 540

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cccgaggtgc tgagcaagaa agagcacagt ttcgaggtgg atgtgtggtc cattgggtgt 780
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<210> 186

<211> 603

<212> PRT

<213> Homo sapiens

<400> 186

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Ala Ala Pro Ala Lys Glu Ile Pro Glu Val Leu Val Asp Pro Arg
35          40          45
Ser Arg Arg Arg Tyr Val Arg Gly Arg Phe Leu Gly Lys Gly Gly Phe
50          55          60
Ala Lys Cys Phe Glu Ile Ser Asp Ala Asp Thr Lys Glu Val Phe Ala
65          70          75          80
Gly Lys Ile Val Pro Lys Ser Leu Leu Lys Pro His Gln Arg Glu
85          90          95
Lys Met Ser Met Glu Ile Ser Ile His Arg Ser Leu Ala His Gln His
100         105         110
Val Val Gly Phe His Gly Phe Phe Glu Asp Asn Asp Phe Val Phe Val
115         120         125
Val Leu Glu Leu Cys Arg Arg Arg Ser Leu Leu Glu Pro His Lys Arg
130         135         140
Arg Lys Ala Leu Thr Glu Pro Glu Ala Arg Tyr Tyr Leu Arg Gln Ile
145         150         155         160
Val Leu Gly Cys Gln Tyr Leu His Arg Asn Arg Val Ile His Arg Asp
165         170         175
Leu Lys Leu Gly Asn Leu Phe Leu Asn Glu Asp Leu Glu Val Lys Ile
180         185         190
Gly Asp Phe Gly Leu Ala Thr Lys Val Glu Tyr Asp Gly Glu Arg Lys

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195					200					205						
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210					215					220						
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225					230					235					240	
Met	Tyr	Thr	Leu	Leu	Val	Gly	Lys	Pro	Pro	Phe	Glu	Thr	Ser	Cys	Leu	
245					250					255						
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260					265					270						
His	Ile	Asn	Pro	Val	Ala	Ala	Ser	Leu	Ile	Gln	Lys	Met	Leu	Gln	Thr	
275					280					285						
Asp	Pro	Thr	Ala	Arg	Pro	Thr	Ile	Asn	Glu	Leu	Leu	Asn	Asp	Glu	Phe	
290					295					300						
Phe	Thr	Ser	Gly	Tyr	Ile	Pro	Ala	Arg	Leu	Pro	Ile	Thr	Cys	Leu	Thr	
305					310					315					320	
Ile	Pro	Pro	Arg	Phe	Ser	Ile	Ala	Pro	Ser	Ser	Leu	Asp	Pro	Ser	Asn	
325					330					335						
Arg	Lys	Pro	Leu	Thr	Val	Leu	Asn	Lys	Gly	Leu	Glu	Asn	Pro	Leu	Pro	
340					345					350						
Glu	Arg	Pro	Arg	Glu	Lys	Glu	Glu	Pro	Val	Val	Arg	Glu	Thr	Gly	Glu	
355					360					365						
Val	Val	Asp	Cys	His	Leu	Ser	Asp	Met	Leu	Gln	Gln	Leu	His	Ser	Val	
370					375					380						
Asn	Ala	Ser	Lys	Pro	Ser	Glu	Arg	Gly	Leu	Val	Arg	Gln	Glu	Glu	Ala	
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Glu	Asp	Pro	Ala	Cys	Ile	Pro	Ile	Phe	Trp	Val	Ser	Lys	Trp	Val	Asp	
405					410					415						
Tyr	Ser	Asp	Lys	Tyr	Gly	Leu	Gly	Tyr	Gln	Leu	Cys	Asp	Asn	Ser	Val	
420					425					430						
Gly	Val	Leu	Phe	Asn	Asp	Ser	Thr	Arg	Leu	Ile	Leu	Tyr	Asn	Asp	Gly	
435					440					445						
Asp	Ser	Leu	Gln	Tyr	Ile	Glu	Arg	Asp	Gly	Thr	Glu	Ser	Tyr	Leu	Thr	
450					455					460						
Val	Ser	Ser	His	Pro	Asn	Ser	Leu	Met	Lys	Lys	Ile	Thr	Leu	Leu	Lys	
465					470					475					480	
Tyr	Phe	Arg	Asn	Tyr	Met	Ser	Glu	His	Leu	Leu	Lys	Ala	Gly	Ala	Asn	
485					490					495						
Ile	Thr	Pro	Arg	Glu	Gly	Asp	Glu	Leu	Ala	Arg	Leu	Pro	Tyr	Leu	Arg	
500					505					510						
Thr	Trp	Phe	Arg	Thr	Arg	Ser	Ala	Ile	Ile	Leu	His	Leu	Ser	Asn	Gly	
515					520					525						
Ser	Val	Gln	Ile	Asn	Phe	Phe	Gln	Asp	His	Thr	Lys	Leu	Ile	Leu	Cys	
530					535					540						
Pro	Leu	Met	Ala	Ala	Val	Thr	Tyr	Ile	Asp	Glu	Lys	Arg	Asp	Phe	Arg	
545					550					555					560	
Thr	Tyr	Arg	Leu	Ser	Leu	Leu	Glu	Glu	Tyr	Gly	Cys	Cys	Lys	Glu	Leu	
565					570					575						
Ala	Ser	Arg	Leu	Arg	Tyr	Ala	Arg	Thr	Met	Val	Asp	Lys	Leu	Leu	Ser	
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<210> 187

<211> 2617

<212> DNA

<213> Homo sapiens

<400> 187


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<210> 188

<211> 743

<212> PRT

<213> Homo sapiens

<400> 188

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      20             25             30
Asp Pro Asn Asp Val Arg Pro Ile Gln Ala Arg Leu Leu Ala Leu Ser
      35             40             45
Gly Pro Gly Gly Gly Arg Gly Arg Gly Ser Leu Leu Leu Arg Arg Gly
      50             55             60

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Phe	Ser	Asp	Ser	Gly	Gly	Pro	Pro	Ala	Lys	Gln	Arg	Asp	Leu	Glu	Gly	65	70	75	80
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Gln	Glu	Ser	Asp	Pro	Glu	Asp	Asp	Asp	Val	Lys	Lys	Pro	Ala	Leu	Gln	100	105	110	
Ser	Ser	Val	Val	Ala	Thr	Ser	Lys	Glu	Arg	Thr	Arg	Arg	Asp	Leu	Ile	115	120	125	
Gln	Asp	Gln	Asn	Met	Asp	Glu	Lys	Gly	Lys	Gln	Arg	Asn	Arg	Arg	Ile	130	135	140	
Phe	Gly	Leu	Leu	Met	Gly	Thr	Leu	Gln	Lys	Phe	Lys	Gln	Glu	Ser	Thr	145	150	155	160
Val	Ala	Thr	Glu	Arg	Gln	Asn	Arg	Arg	Gln	Glu	Ile	Glu	Gln	Lys	Leu	165	170	175	
Glu	Val	Gln	Ala	Glu	Glu	Glu	Arg	Lys	Gln	Val	Glu	Asn	Glu	Arg	Arg	180	185	190	
Glu	Leu	Phe	Glu	Glu	Arg	Arg	Ala	Lys	Gln	Thr	Glu	Leu	Arg	Leu	Leu	195	200	205	
Glu	Gln	Lys	Val	Glu	Leu	Ala	Gln	Leu	Gln	Glu	Glu	Trp	Asn	Glu	His	210	215	220	
Asn	Ala	Lys	Ile	Ile	Lys	Tyr	Ile	Arg	Thr	Lys	Thr	Lys	Pro	His	Leu	225	230	235	240
Phe	Tyr	Ile	Pro	Gly	Arg	Met	Cys	Pro	Ala	Thr	Gln	Lys	Leu	Ile	Glu	245	250	255	
Glu	Ser	Gln	Arg	Lys	Met	Asn	Ala	Leu	Phe	Asp	Gly	Arg	Arg	Ile	Glu	260	265	270	
Phe	Ala	Glu	Gln	Ile	Asn	Lys	Met	Glu	Ala	Arg	Pro	Arg	Arg	Gln	Ser	275	280	285	
Met	Lys	Glu	Lys	Glu	His	Gln	Val	Val	Arg	Asn	Glu	Glu	His	Lys	Ala	290	295	300	
Glu	Gln	Glu	Glu	Gly	Lys	Val	Ala	Gln	Arg	Glu	Glu	Glu	Leu	Val	Glu	305	310	315	320
Thr	Gly	Asn	Gln	His	Asn	Asp	Val	Glu	Ile	Glu	Glu	Ala	Gly	Glu	Glu	325	330	335	
Glu	Glu	Lys	Glu	Ile	Gly	Ile	Val	His	Ser	Asp	Ala	Glu	Lys	Glu	Gln	340	345	350	
Glu	Glu	Glu	Glu	Gln	Lys	Gln	Glu	Met	Glu	Val	Lys	Met	Glu	Glu	Glu	355	360	365	
Thr	Glu	Val	Arg	Glu	Ser	Glu	Lys	Gln	Gln	Asp	Ser	Gln	Pro	Glu	Glu	370	375	380	
Val	Met	Asp	Val	Leu	Glu	Met	Val	Glu	Asn	Val	Lys	His	Val	Ile	Ala	385	390	395	400
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Glu	Asn	Glu	Ala	Ser	Lys	Glu	Leu	Glu	Pro	Glu	Met	Glu	Phe	Glu	Ile	420	425	430	
Glu	Pro	Asp	Lys	Glu	Cys	Lys	Ser	Leu	Ser	Pro	Gly	Lys	Glu	Asn	Val	435	440	445	
Ser	Ala	Leu	Asp	Met	Glu	Lys	Glu	Ser	Asp	Glu	Lys	Glu	Glu	Lys	Glu	450	455	460	
Ser	Glu	Pro	Gln	Pro	Glu	Pro	Val	Ala	Gln	Pro	Gln	Ala	Gln	Ser	Gln	465	470	475	480
Pro	Gln	Leu	Gln	Leu	Gln	Ser	Gln	Ser	Glu	Pro	Gln	Pro	Gln	Leu	Gln	485	490	495	
Pro	Glu	Pro	Ala	Gln	Pro	Gln	Leu	Gln	Ser	Gln	Pro	Gln	Leu	Gln	Leu	500	505	510	
Gln	Ser	Gln	Cys	His	Ala	Val	Leu	Gln	Ser	His	Pro	Pro	Ser	Gln	Pro	515	520	525	
Glu	Asp	Leu	Ser	Leu	Ala	Val	Leu	Gln	Pro	Thr	Pro	Gln	Val	Thr	Gln				

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Glu His Gly His Phe Leu	Pro Glu Arg Lys Asp	Phe Pro Val Glu Ser		
545	550	555	560	
Val Lys Leu Thr Glu Val	Pro Val Asp Pro Val	Leu Thr Val His Pro		
	565	570	575	
Glu Ser Glu Ser Glu Thr	Asn Thr Arg Ser Arg	Ser Arg Gly Arg Thr		
	580	585	590	
Arg Asn Arg Thr Thr Lys	Ser Arg Ser Ser Ser	Ser Ser Ser Ser		
	595	600	605	
Ser Ser Ser Ser Ser Thr	Ser Ser Ser Ser Gly	Ser Ser Ser Ser Ser		
	610	615	620	
Gly Ser Ser Ser Ser Arg	Ser Ser Ser Ser Ser	Ser Ser Ser Thr Ser		
625	630	635	640	
Gly Ser Ser Ser Arg Asp	Ser Ser Ser Ser Thr	Ser Ser Ser Ser Ser		
	645	650	655	
Ser Arg Ser Arg Ser Arg	Gly Arg Gly His Asn	Arg Asp Arg Lys His		
	660	665	670	
Arg Arg Ser Val Asp Arg	Lys Arg Arg Asp Thr	Ser Gly Leu Glu Arg		
	675	680	685	
Ser His Lys Ser Ser Lys	Gly Gly Ser Ser Arg	Asp Thr Lys Gly Ser		
	690	695	700	
Lys Asp Lys Asn Ser Arg	Ser Asp Arg Lys Arg	Ser Ile Ser Glu Ser		
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Ser Arg Ser Gly Lys Arg	Ser Ser Arg Ser Glu	Arg Asp Arg Lys Ser		
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Asp Arg Lys Asp Lys Arg	Arg			
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<210> 189
 <211> 1182
 <212> DNA
 <213> Homo sapiens

<400> 189
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 gccaggtagc aatgggtgcg ctgcaatcca gacagtaatt ctgcaaactg ccttgagaga 180
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<210> 190
 <211> 158
 <212> PRT

<213> Homo sapiens

<400> 190

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Met Met Gln Lys Leu Leu Lys Cys Ser Arg Leu Val Leu Ala Leu Ala
 1           5           10           15
Leu Ile Leu Val Leu Glu Ser Ser Val Gln Gly Tyr Pro Thr Gln Arg
      20           25           30
Ala Arg Tyr Gln Trp Val Arg Cys Asn Pro Asp Ser Asn Ser Ala Asn
      35           40           45
Cys Leu Glu Glu Lys Gly Pro Met Phe Glu Leu Leu Pro Gly Glu Ser
      50           55           60
Asn Lys Ile Pro Arg Leu Arg Thr Asp Leu Phe Pro Lys Thr Arg Ile
      65           70           75           80
Gln Asp Leu Asn Arg Ile Phe Pro Leu Ser Glu Asp Tyr Ser Gly Ser
      85           90           95
Gly Phe Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Phe
      100          105          110
Leu Thr Glu Met Glu Gln Asp Tyr Gln Leu Val Asp Glu Ser Asp Ala
      115          120          125
Phe His Asp Asn Leu Arg Ser Leu Asp Arg Asn Leu Pro Ser Asp Ser
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<210> 191

<211> 1595

<212> DNA

<213> Homo sapiens

<400> 191

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 <211> 175
 <212> PRT
 <213> Homo sapiens

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 35 40 45
 Lys Ser Ile Gln Asp Leu Arg Arg Phe Phe Leu His His Leu Ile
 50 55 60
 Ala Glu Ile His Thr Ala Glu Ile Arg Ala Thr Ser Glu Val Ser Pro
 65 70 75 80
 Asn Ser Lys Pro Ser Pro Asn Thr Lys Asn His Pro Val Arg Phe Gly
 85 90 95
 Ser Asp Asp Glu Gly Arg Tyr Leu Thr Gln Glu Thr Asn Lys Val Glu
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 Thr Tyr Lys Glu Gln Pro Leu Lys Thr Pro Gly Lys Lys Lys Gly
 115 120 125
 Lys Pro Gly Lys Arg Lys Glu Gln Glu Lys Lys Lys Arg Arg Thr Arg
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<210> 193
 <211> 2657
 <212> DNA
 <213> Homo sapiens

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<210> 194

<211> 168

<212> PRT

<213> Homo sapiens

<400> 194

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          20          25          30
Gly Lys Lys Glu Lys Pro Glu Lys Lys Val Lys Lys Ser Asp Cys Gly
          35          40          45
Glu Trp Gln Trp Ser Val Cys Val Pro Thr Ser Gly Asp Cys Gly Leu
          50          55          60
Gly Thr Arg Glu Gly Thr Arg Thr Gly Ala Glu Cys Lys Gln Thr Met
          65          70          75          80
Lys Thr Gln Arg Cys Lys Ile Pro Cys Asn Trp Lys Lys Gln Phe Gly
          85          90          95
Ala Glu Cys Lys Tyr Gln Phe Gln Ala Trp Gly Glu Cys Asp Leu Asn
          100          105          110
Thr Ala Leu Lys Thr Arg Thr Gly Ser Leu Lys Arg Ala Leu His Asn
          115          120          125
Ala Glu Cys Gln Lys Thr Val Thr Ile Ser Lys Pro Cys Gly Lys Leu
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<210> 195

<211> 2972

<212> DNA

<213> Homo sapiens

<400> 195

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<211> 890

<212> PRT

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Val	Lys	Val	Tyr	Leu	Arg	Val	Arg	Pro	Leu	Leu	Pro	Ser	Glu	Leu	Glu
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Val	Ala	Lys	Phe	Ser	Ala	Ile	Ala	Ser	Gln	Leu	Val	His	Ala	Pro	Pro
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				565					570					575	
Glu	Arg	Gln	Glu	Lys	Leu	Gln	Leu	Glu	Met	His	Leu	Arg	Asp	Glu	Ile
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Cys	Asn	Glu	Met	Val	Glu	Gln	Met	Gln	Gln	Arg	Glu	Gln	Trp	Cys	Ser
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Ile	Gln	Glu	Arg	Asp	Glu	Lys	Ile	Glu	Glu	Leu	Glu	Ala	Leu	Leu	Gln
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Glu	Ala	Arg	Gln	Gln	Ser	Val	Ala	His	Gln	Gln	Ser	Gly	Ser	Glu	Leu
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Ala	Leu	Arg	Arg	Ser	Gln	Arg	Leu	Ala	Ala	Ser	Ala	Ser	Thr	Gln	Gln
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Ser	Thr	Thr	Glu	Glu	Leu	His	Lys	Tyr	Gln	Lys	Met	Leu	Glu	Pro	Pro
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Pro	Ser	Ala	Lys	Pro	Phe	Thr	Ile	Asp	Val	Asp	Lys	Lys	Leu	Glu	Glu
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Gly	Lys	Leu	Arg	Gln	Ala	Leu	Thr	Thr	Cys	Asp	Asp	Ile	Leu	Ile	Lys
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			820					825					830		
Asn	Gln	Glu	Asn	Gln	Gln	Pro	Asn	Gln	Gln	Pro	Pro	Gly	Lys	Lys	Pro
			835				840					845			
Phe	Leu	Arg	Asn	Leu	Leu	Pro	Arg	Thr	Pro	Thr	Cys	Gln	Ser	Ser	Thr
			850			855					860				
Asp	Cys	Ser	Pro	Tyr	Ala	Arg	Ile	Leu	Arg	Ser	Arg	Arg	Ser	Pro	Leu
865					870					875					880
Leu	Lys	Ser	Gly	Pro	Phe	Gly	Lys	Lys	Tyr						
				885					890						

<211> 768
 <212> DNA
 <213> Homo sapiens

<400> 197
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 ctatgagcac tggggcctgt atataggaga tggctacgtg atccatctgg ctccccaag 180
 tgagtacccc ggggctgggt cctccagtgt cttctcagtc ctgagcaaca gtgcagaggt 240
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 ggaccatgag taccaaccac ggcccgtgga ggtgatcatc agttctgcga aggagatggt 360
 tggtcagaag atgaagtaca gtattgtgag caggaactgt gagcactttg tcgccagct 420
 gagatatggc aagtcccgtt gtaaacaggt ggaaaaggcc aaggttgaag tcggtgtggc 480
 cacggcgctt ggaatcctgg ttgttgctgg atgctctttt gcgattagga gataccaaaa 540
 aaaagcaaca gcctgaagca gccacaaaat cctgtgttag aagcagctgt ggggtccca 600
 gtggagatga gcctcccca tgctccagc agcctgaccc tcgtgccctg tctcaggcgt 660
 tctctagatc ctttctctctg ttccctctc tcgctggcaa aagtatgatc taattgaaac 720
 aagactgaag gatcaataaa cagccatctg ccccttcaaa aaaaaaaaa 768

<210> 198
 <211> 164
 <212> PRT
 <213> Homo sapiens

<400> 198
 Met Ala Ser Pro His Gln Glu Pro Lys Pro Gly Asp Leu Ile Glu Ile
 1 5 10 15
 Phe Arg Leu Gly Tyr Glu His Trp Ala Leu Tyr Ile Gly Asp Gly Tyr
 20 25 30
 Val Ile His Leu Ala Pro Pro Ser Glu Tyr Pro Gly Ala Gly Ser Ser
 35 40 45
 Ser Val Phe Ser Val Leu Ser Asn Ser Ala Glu Val Lys Arg Gly Arg
 50 55 60
 Leu Glu Asp Val Val Gly Gly Cys Cys Tyr Arg Val Asn Asn Ser Leu
 65 70 75 80
 Asp His Glu Tyr Gln Pro Arg Pro Val Glu Val Ile Ile Ser Ser Ala
 85 90 95
 Lys Glu Met Val Gly Gln Lys Met Lys Tyr Ser Ile Val Ser Arg Asn
 100 105 110
 Cys Glu His Phe Val Ala Gln Leu Arg Tyr Gly Lys Ser Arg Cys Lys
 115 120 125
 Gln Val Glu Lys Ala Lys Val Glu Val Gly Val Ala Thr Ala Leu Gly
 130 135 140
 Ile Leu Val Val Ala Gly Cys Ser Phe Ala Ile Arg Arg Tyr Gln Lys
 145 150 155 160
 Lys Ala Thr Ala

<210> 199
 <211> 720
 <212> DNA
 <213> Homo sapiens

<400> 199
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 gctgtcccgg cagtctccag ccgtcccgcc cgcttggtggc caaactggct ccagtcactc 120
 ccgaaatgcc agtcgacttc actgggtact ggaagatgtt ggtcaacgag aatttcgagg 180
 agtacctgcg cgccctcgac gtcaatgtgg ccttgcgcaa aatcgccaac ttgctgaagc 240

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cagacaaaga gatcgtgcag gacggtgacc atatgatcat ccgcacgctg agcactttta 300
ggaactacat catggacttc caagttggga aggagtttga ggaggatctg acaggcatag 360
atgaccgcaa gtgcatgaca acagtgaact gggacggaga caagctccag tgtgtgcaga 420
agggtgagaa ggaggggagc ggctggaccc agtggatcga gggatgatgag ctgcacctag 480
agatgagagt ggaaggtgtg gtctgcaagc aagtattcaa gaaggtgcag tgaggcccaa 540
gcagacaacc ttgtcccaac caatcagcag gatgtgtgag ccaggatccc tctttgcaca 600
gcatgaggca aaaatgtcca gccacccta ggcattctgt agcagagtct gtctcttggc 660
tttgtcactt ttccttttct taaaacaaag ccatgccaat aaagtgcact gtgttcaaaa 720

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<210> 200

<211> 135

<212> PRT

<213> Homo sapiens

<400> 200

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Met Pro Val Asp Phe Thr Gly Tyr Trp Lys Met Leu Val Asn Glu Asn
 1          5          10          15
Phe Glu Glu Tyr Leu Arg Ala Leu Asp Val Asn Val Ala Leu Arg Lys
      20          25          30
Ile Ala Asn Leu Leu Lys Pro Asp Lys Glu Ile Val Gln Asp Gly Asp
      35          40          45
His Met Ile Ile Arg Thr Leu Ser Thr Phe Arg Asn Tyr Ile Met Asp
      50          55          60
Phe Gln Val Gly Lys Glu Phe Glu Glu Asp Leu Thr Gly Ile Asp Asp
      65          70          75          80
Arg Lys Cys Met Thr Thr Val Ser Trp Asp Gly Asp Lys Leu Gln Cys
      85          90          95
Val Gln Lys Gly Glu Lys Glu Gly Arg Gly Trp Thr Gln Trp Ile Glu
      100          105          110
Gly Asp Glu Leu His Leu Glu Met Arg Val Glu Gly Val Val Cys Lys
      115          120          125
Gln Val Phe Lys Lys Val Gln
      130          135

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<210> 201

<211> 2383

<212> DNA

<213> Homo sapiens

<400> 201

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ccacctgcct ggagagagcc aaagagttca agacacgtct ggggatcttt cttcacaaaat 180
cagagctggg ctgcgatact gggagtactg gcaagtccga gtggggcagt aaacacagca 240
aagagaatag aaactttctca gaagatgtgc tgggggtggag agagtcgttc gacctgctgc 300
tgagcagtaa aaatggagtg gctgccttcc acgcttttct gaagacagag ttcagtgagg 360
agaacctgga gttctggctg gcctgtgagg agttcaagaa gatccgatca gctaccaagc 420
tggcctccag ggcacaccag atctttgagg agttcatttg cagtgaggcc cctaaagagg 480
tcaacattga ccatgagacc cgcgagctga cgaggatgaa cctgcagact gccacagcca 540
catgctttga tgcggctcag gggaagacac gtaccctgat ggagaaggac tcttaccac 600
gcttcctgaa gtgcctgtgt taccgggacc tggctgcccc agcctcagcc gcctctgccca 660
ctctgtccag ctgcagcctg gacgagccct cacacacctg agtctccacg gcagtggagg 720
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gagaggagcc gccacttcc aggacctgtg aataagggt aatgatgagg gttggtgggg 960
ctctctgtgg ggcaaaaagg tggatatggg gttagcactg gctctcgttc tcaccggaga 1020

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aggaagtgtt ctagtgtggt ttaggaaaca tgtggataaa gggaaccatg aaaatgagag 1080
gaggaaagac atccagatca gctgttttgc ctgttgctca gttgactctg attgcatcct 1140
gttttcctaa ttcccagact gttctgggca cggaaggac cctggatgtg gagtcttccc 1200
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cactcctgtg tgtctgtcca gccttgcaag catgtcaagg ccagcaagct gatgtgactc 1320
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ggagagccct gaaaggaggc tcacttgaat ccagctcagt gctctgggtg gccccctgca 1440
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tcttcctgga tgtgccctct ctgagttctg tgcgtgtctt tggaggcagg gccaggaga 1560
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aaggcagaaa aggatcctag gaaataagtc tcttggcggg ccctgagagt cctgctgaaa 1680
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caggaccatg gcacccttag agtgcagaag ctggggggag aggctgcttc gaagggcagg 1860
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<210> 202

<211> 202

<212> PRT

<213> Homo sapiens

<400> 202

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Met Cys Arg Thr Leu Ala Ala Phe Pro Thr Thr Cys Leu Glu Arg Ala
 1          5          10          15
Lys Glu Phe Lys Thr Arg Leu Gly Ile Phe Leu His Lys Ser Glu Leu
 20          25          30
Gly Cys Asp Thr Gly Ser Thr Gly Lys Ser Glu Trp Gly Ser Lys His
 35          40          45
Ser Lys Glu Asn Arg Asn Phe Ser Glu Asp Val Leu Gly Trp Arg Glu
 50          55          60
Ser Phe Asp Leu Leu Leu Ser Ser Lys Asn Gly Val Ala Ala Phe His
 65          70          75          80
Ala Phe Leu Lys Thr Glu Phe Ser Glu Glu Asn Leu Glu Phe Trp Leu
 85          90          95
Ala Cys Glu Glu Phe Lys Lys Ile Arg Ser Ala Thr Lys Leu Ala Ser
100          105          110
Arg Ala His Gln Ile Phe Glu Glu Phe Ile Cys Ser Glu Ala Pro Lys
115          120          125
Glu Val Asn Ile Asp His Glu Thr Arg Glu Leu Thr Arg Met Asn Leu
130          135          140
Gln Thr Ala Thr Ala Thr Cys Phe Asp Ala Ala Gln Gly Lys Thr Arg
145          150          155          160
Thr Leu Met Glu Lys Asp Ser Tyr Pro Arg Phe Leu Lys Ser Pro Ala
165          170          175
Tyr Arg Asp Leu Ala Ala Gln Ala Ser Ala Ala Ser Ala Thr Leu Ser
180          185          190
Ser Cys Ser Leu Asp Glu Pro Ser His Thr
195          200

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<210> 203

<211> 616
 <212> DNA
 <213> Homo sapiens

<400> 203
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 tccacaagta ctctgccaag gagggcgaca agttcaagct gagtaagggg gaaatgaagg 180
 aacttctgca caaggagctg cccagctttg tggggcattc cagagaacca tgtgctgtga 240
 gggccttccg agtccatctg tttaatcctg tcattggaga cttgagaaac cagagcccag 300
 aagggaaaag tgattgtccc aagatcacac agcactggag aaagtggatg aggaggggct 360
 gaagaagctg atgggcagcc tggatgagaa cagtgaccag caggtggact tccaggagta 420
 tgctgttttc ctggcactca tcaactgtcat gtgcaatgac ttcttccagg gctgcccaga 480
 ccgacctga agcagaactc ttgacttcct gccatggatc tcttgggccc aggactgttg 540
 atgcctttga gttttgtatt caataaactt tttttgtctg ttgaaaaaaa aaaaaaaaaa 600
 aaaaaaaaaa aaaaaa 616

<210> 204
 <211> 96
 <212> PRT
 <213> Homo sapiens

<400> 204
 Met Met Cys Ser Ser Leu Glu Gln Ala Leu Ala Val Leu Val Thr Thr
 1 5 10 15
 Phe His Lys Tyr Ser Cys Gln Glu Gly Asp Lys Phe Lys Leu Ser Lys
 20 25 30
 Gly Glu Met Lys Glu Leu Leu His Lys Glu Leu Pro Ser Phe Val Gly
 35 40 45
 His Ser Arg Glu Pro Cys Ala Val Arg Ala Phe Arg Val His Leu Phe
 50 55 60
 Asn Pro Val Ile Gly Asp Leu Arg Asn Gln Ser Pro Glu Gly Lys Ser
 65 70 75 80
 Asp Cys Pro Lys Ile Thr Gln His Trp Arg Lys Trp Met Arg Arg Gly
 85 90 95

<210> 205
 <211> 428
 <212> DNA
 <213> Homo sapiens

<400> 205
 ctgggtctgt ctctgccacc tgggtctgcc cagatccatg atgtgcagtt ctctggagca 60
 ggcgtggct gtgctgggtca ctaccttcca caagtactcc tgccaagagg ggcacaagtt 120
 caagctgagt aagggggaaa tgaaggaact tctgcacaag gagctgcca gctttgtggg 180
 ggagaaaagt gatgaggagg ggctgaagaa gctgatgggc agcctggatg agaacagtga 240
 ccagcaggtg gacttccagg agtatgctgt tttcctggca ctcatcactg tcatgtgcaa 300
 tgacttcttc cagggctgcc cagaccgacc ctgaagcaga actcttgact tcctgccatg 360
 gatctcttgg gcccaggact gttgatgcct ttgagttttg tattcaataa actttttttg 420
 tctgttga 428

<210> 206
 <211> 97
 <212> PRT
 <213> Homo sapiens

<400> 206
 Met Cys Ser Ser Leu Glu Gln Ala Leu Ala Val Leu Val Thr Thr Phe

270

1	5	10	15
His Lys Tyr Ser Cys Gln Glu Gly Asp Lys Phe Lys Leu Ser Lys Gly			
	20	25	30
Glu Met Lys Glu Leu Leu His Lys Glu Leu Pro Ser Phe Val Gly Glu			
	35	40	45
Lys Val Asp Glu Glu Gly Leu Lys Lys Leu Met Gly Ser Leu Asp Glu			
	50	55	60
Asn Ser Asp Gln Gln Val Asp Phe Gln Glu Tyr Ala Val Phe Leu Ala			
65	70	75	80
Leu Ile Thr Val Met Cys Asn Asp Phe Phe Gln Gly Cys Pro Asp Arg			
	85	90	95
Pro			

<210> 207

<211> 799

<212> DNA

<213> Homo sapiens

<400> 207

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cactcccaaa gaactgggta ctcaacactg agcagatctg ttctttgagc taaaaaccat 60
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cggcgaatca gaagcagcaa gcaactttga ctgctgtctt ggatacacag accgtattct 180
tcatcctaaa ttatttgtgg gcttcacacg gcagctggcc aatgaaggct gtgacatcaa 240
tgctatcatc ttccacacaa agaaaaagtt gtctgtgtgc gcaaatccaa aacagacttg 300
ggtgaaatat attgtgcgtc tcctcagtaa aaaagtcaag aacatgtaaa aactgtggct 360
tttctggaat ggaattggac atagcccaag aacagaaaga accttgctgg ggttggaggt 420
ttcacttgca catcatggag ggttttagtc ttatctaatt tgtgcctcac tggacttgtc 480
caattaatga agttgattca tattgcatca tagtttgctt tgtttaagca tcacattaaa 540
gttaaaactgt attttatgtt atttatagct gtaggttttc tgtgttttagc tatttaatac 600
taattttcca taagctatct tggtttagtg caaagtataa aattatattt gggggggaat 660
aagattatat ggactttctt gcaagcaaca agctatcttt taaaaaaaact atttaacatt 720
cttttgttta tattgttttg tctcctaaat tgttgtaatt gcattataaa ataagaaaaa 780
cattaataag acaaatattt                                     799

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<210> 208

<211> 96

<212> PRT

<213> Homo sapiens

<400> 208

Met Cys Cys Thr Lys Ser Leu Leu Leu Ala Ala Leu Met Ser Val Leu	
1	15
Leu Leu His Leu Cys Gly Glu Ser Glu Ala Ala Ser Asn Phe Asp Cys	
	30
Cys Leu Gly Tyr Thr Asp Arg Ile Leu His Pro Lys Phe Ile Val Gly	
	45
Phe Thr Arg Gln Leu Ala Asn Glu Gly Cys Asp Ile Asn Ala Ile Ile	
	60
Phe His Thr Lys Lys Lys Leu Ser Val Cys Ala Asn Pro Lys Gln Thr	
65	80
Trp Val Lys Tyr Ile Val Arg Leu Leu Ser Lys Lys Val Lys Asn Met	
	95

<210> 209

<211> 2133

<212> DNA

<213> Homo sapiens

<400> 209

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gaagccctgc ctgatgagac agaggtggtg gaagaaactg tggcagaggt gactgaggta 180
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acatttggtt tagtgtcata aggttttttag catgttcctc cttttcttca cccctccctt 1920
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ctgaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa 2133

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<210> 210

<211> 303

<212> PRT

<213> Homo sapiens

<400> 210

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Met Arg Ala Trp Ile Phe Phe Leu Leu Cys Leu Ala Gly Arg Ala Leu
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Ala Ala Pro Gln Gln Glu Ala Leu Pro Asp Glu Thr Glu Val Val Glu
 20           25           30
Glu Thr Val Ala Glu Val Thr Glu Val Ser Val Gly Ala Asn Pro Val
 35           40           45
Gln Val Glu Val Gly Glu Phe Asp Asp Gly Ala Glu Glu Thr Glu Glu
 50           55           60
Glu Val Val Ala Glu Asn Pro Cys Gln Asn His His Cys Lys His Gly
 65           70           75           80
Lys Val Cys Glu Leu Asp Glu Asn Asn Thr Pro Met Cys Val Cys Gln
 85           90           95
Asp Pro Thr Ser Cys Pro Ala Pro Ile Gly Glu Phe Glu Lys Val Cys

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<210> 211
<211> 2228
<212> DNA
<213> Homo sapiens
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<400> 211						
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cctactccta	aagtgtattg	tattgatctt	ggcaccacct	attgttctgt	tgggggtgtt	180
tttcctggca	caggaaaagt	aaagtgatt	ccagatgaa	atgggcatat	cagcatatccc	240
agcatgtgtg	cttttactga	caatgatgta	tctgtgggat	atgaaacgct	agagctggca	300
gattcaaatc	ctcaaaacac	aatatatgat	gccaaaagat	tcataggcaa	gatttttacc	360
gcagaagagt	tggaggctga	aattggcaga	tacctattta	aggtttttaa	caaaaatgga	420
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tctcgactat	tgttgaagtt	aaaggaaatg	gcagaggcat	atcttggaat	gccagttgcc	540
aatgctgtca	tttctgtacc	agcagaattt	gatctaaaa	agagaaattc	aacaattgaa	600
ctgtctaacc	tgcaggact	gaagattttg	agggtaataa	atgaaccac	agcagcagct	660
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tctggaaca	ataaacttgg	aggacaggac	ttcaatcaga	gattgcttca	gtacttatat	840
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gtattactaa	cggtggagga	gcaggacagg	aaggaacctc	acagtagtga	cactgaactg	1020
ccaaaagaca	aactttcctc	agcagatgac	catcgctga	acagtggtgt	tggacgtggc	1080
ctttctgata	agaaaaagtg	agaaagtcag	gttttatttg	aaacagaaat	atcacggaaa	1140
ctctttgata	cccttaatga	agacctcttt	cagaaaatac	tggtagccat	tcagcaagta	1200
ttgaaagaag	gccacctgga	aaagactgag	attgatgagg	tggttttagt	tgggggctcc	1260
actcgtattc	ctcggatccg	tcaagtcat	caagagttct	ttggaaaaga	tccaacaca	1320
tctgtagacc	ctgacctagc	agtagtaacg	ggagtggcta	tccaagcagg	gattgatgga	1380
ggctctttgc	ctctccaagt	cagtgtctta	gaaattcccc	ataagcattt	acaaaaaac	1440
aacttcaact	gaattctgca	gaataataatg	tattttgtga	acttgtctga	tgatctcttc	1500
ccatttatca	gattaccttt	tccacaaaag	aaagtctcta	aaatatcaca	gatttaccta	1560


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gagggcaaca tttagatata ggaaaatttt acatagtgtt ttgtcttagg attagacgtg 1620
accagattga tcctgtttga ttttggagag atcctattct aacaaatact ctaaaatgat 1680
aaaattgagg tacaactctc ttaaaagagt atggataact atattttctg gattctggag 1740
gttgataacc atatgcactt aacattatat tctataaaca ttaagtagtg ccagttatga 1800
gattcccgagt tcttactaaa ttgtatttagc aggagctggg aattacttgt attatcacat 1860
gtaactaata atttgaacta tacttgaagg accgtgttga tgtcagggtat ttacagtggg 1920
tggaagatag cagtattatt agcataagct gcatacgtaa tattcagtaa ctgccatatt 1980
atataacaaa tttacattca caaattcagt atcctgttaa gtgtcatatt cttgtaatct 2040
gcattctcca ggagttttat gtgtttaata gatgaattta ttttatttct aaagggtattc 2100
aaatgtttca gcaccatata atagaaatac ccaattatat tctagtctct ttatgtcctg 2160
tacatcattc tctgcttgga tttccattat tctgtttggg tagagaataa aattgggtaat 2220
tgcatattg                                     2228

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<210> 212

<211> 471

<212> PRT

<213> Homo sapiens

<400> 212

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Met Ala Arg Glu Met Thr Ile Leu Gly Ser Ala Val Leu Thr Leu Leu
1          5          10          15
Leu Ala Gly Tyr Leu Ala Gln Gln Tyr Leu Pro Leu Pro Thr Pro Lys
20          25          30
Val Ile Gly Ile Asp Leu Gly Thr Thr Tyr Cys Ser Val Gly Val Phe
35          40          45
Phe Pro Gly Thr Gly Lys Val Lys Val Ile Pro Asp Glu Asn Gly His
50          55          60
Ile Ser Ile Pro Ser Met Val Ser Phe Thr Asp Asn Asp Val Tyr Val
65          70          75          80
Gly Tyr Glu Ser Val Glu Leu Ala Asp Ser Asn Pro Gln Asn Thr Ile
85          90          95
Tyr Asp Ala Lys Arg Phe Ile Gly Lys Ile Phe Thr Ala Glu Glu Leu
100         105         110
Glu Ala Glu Ile Gly Arg Tyr Pro Phe Lys Val Leu Asn Lys Asn Gly
115         120         125
Met Val Glu Phe Ser Val Thr Ser Asn Glu Thr Ile Thr Val Ser Pro
130         135         140
Glu Tyr Val Gly Ser Arg Leu Leu Leu Lys Leu Lys Glu Met Ala Glu
145         150         155         160
Ala Tyr Leu Gly Met Pro Val Ala Asn Ala Val Ile Ser Val Pro Ala
165         170         175
Glu Phe Asp Leu Lys Gln Arg Asn Ser Thr Ile Glu Ala Ala Asn Leu
180         185         190
Ala Gly Leu Lys Ile Leu Arg Val Ile Asn Glu Pro Thr Ala Ala Ala
195         200         205
Met Ala Tyr Gly Leu His Lys Ala Asp Val Phe His Val Leu Val Ile
210         215         220
Asp Leu Gly Gly Gly Thr Leu Asp Val Ser Leu Leu Asn Lys Gln Gly
225         230         235         240
Gly Met Phe Leu Thr Arg Ala Met Ser Gly Asn Asn Lys Leu Gly Gly
245         250         255
Gln Asp Phe Asn Gln Arg Leu Leu Gln Tyr Leu Tyr Lys Gln Ile Tyr
260         265         270
Gln Thr Tyr Gly Phe Val Pro Ser Arg Lys Glu Glu Ile His Arg Leu
275         280         285
Arg Gln Ala Val Glu Met Val Lys Leu Asn Leu Thr Leu His Gln Ser
290         295         300
Ala Gln Leu Ser Val Leu Leu Thr Val Glu Glu Gln Asp Arg Lys Glu
305         310         315         320

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<210> 213
<211> 1224
<212> DNA
<213> Homo sapiens
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<400> 213						
ggccggggaga	gtagcagtg	cttgga	agctctctc	cccccttctc	tctaaggatg	60
gcccaagaag	agaactccta	cccctggccc	tacggccgac	agacggctcc	atctggcctg	120
agcaccctgc	cccagcgagt	cctccggaaa	gagcctgtca	ccccactgtc	acttgtctctc	180
atgagccgct	ccaatgtcca	gcccacagat	gcccctggcc	agaagtgat	ggagaatagc	240
atggggacac	ccgacatctt	aacgcggcac	ttcacaattg	atgactttga	gattgggcgt	300
cctctgggca	aaggcaagtt	tggaaacgtg	tacttggtct	gggagaagaa	aagccatttc	360
atcgtggcgc	tcaaggtcct	cttcaagtcc	cagatagaga	aggagggcgt	ggagcatcag	420
ctgcgcagag	agatcgaaat	ccaggccccac	ctgcaccatc	ccaacatcct	gcgtctctac	480
aactattttt	atgaccggag	gaggatctac	ttgattctag	agtatgccc	cccgggggag	540
ctctacaagg	agctgcagaa	gagctgcaca	tttgacgagc	agcgaacagc	cacgatcatg	600
gaggagttgg	cagatgctct	aatgtactgc	catgggaaga	aggtgattca	cagagacata	660
aagccagaaa	atctgctctt	agggctcaag	ggagagctga	agattgctga	cttcggctgg	720
tctgtgcatg	cgccctccct	gaggaggaag	acaatgtgtg	gcaccttgga	ctacctgccc	780
ccagatagta	ttgaggggcg	catgcacaat	gagaaggtgg	atctgtgtgt	cattgagagt	840
ctttgctatg	agctgtcgtt	ggggaaccca	ccctttgaga	gtgcatcaca	caacgagacc	900
tatcgccgca	togtcaaggt	ggacctaaag	ttccccgctt	ctgtgcccac	gggagcccag	960
gacctcatct	ccaaactgct	caggcataac	ccctcggaac	ggctgcccct	ggcccagggtc	1020
tcagcccacc	cttgggtccg	ggccaactct	cggaggggtgc	tgcctccctc	tgcccttcaa	1080
tctgtcgctc	gatggtccct	gtcatttcact	cgggtgcgtg	tgtttgtatg	tctgtgtatg	1140
tataggggaa	agaagggatc	ctaactgtt	cccttatctg	ttttctacct	cctcctttgt	1200
ttaataaagg	ctqaaagctt	ttgt				1224

```
<210> 214
<211> 344
<212> PRT
<213> Homo sapiens
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<400> 214
Met Ala Gln Lys Glu Asn Ser Tyr Pro Trp Pro Tyr Gly Arg Gln Thr
 1             5             10             15
Ala Pro Ser Gly Leu Ser Thr Leu Pro Gln Arg Val Leu Arg Lys Glu
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	20		25		30										
Pro	Val	Thr	Pro	Ser	Ala	Leu	Val	Leu	Met	Ser	Arg	Ser	Asn	Val	Gln
	35						40						45		
Pro	Thr	Ala	Ala	Pro	Gly	Gln	Lys	Val	Met	Glu	Asn	Ser	Ser	Gly	Thr
	50					55					60				
Pro	Asp	Ile	Leu	Thr	Arg	His	Phe	Thr	Ile	Asp	Asp	Phe	Glu	Ile	Gly
65					70					75				80	
Arg	Pro	Leu	Gly	Lys	Gly	Lys	Phe	Gly	Asn	Val	Tyr	Leu	Ala	Arg	Glu
			85						90					95	
Lys	Lys	Ser	His	Phe	Ile	Val	Ala	Leu	Lys	Val	Leu	Phe	Lys	Ser	Gln
		100						105					110		
Ile	Glu	Lys	Glu	Gly	Val	Glu	His	Gln	Leu	Arg	Arg	Glu	Ile	Glu	Ile
	115						120					125			
Gln	Ala	His	Leu	His	His	Pro	Asn	Ile	Leu	Arg	Leu	Tyr	Asn	Tyr	Phe
	130						135					140			
Tyr	Asp	Arg	Arg	Arg	Ile	Tyr	Leu	Ile	Leu	Glu	Tyr	Ala	Pro	Arg	Gly
145					150					155					160
Glu	Leu	Tyr	Lys	Glu	Leu	Gln	Lys	Ser	Cys	Thr	Phe	Asp	Glu	Gln	Arg
			165						170					175	
Thr	Ala	Thr	Ile	Met	Glu	Glu	Leu	Ala	Asp	Ala	Leu	Met	Tyr	Cys	His
		180							185				190		
Gly	Lys	Lys	Val	Ile	His	Arg	Asp	Ile	Lys	Pro	Glu	Asn	Leu	Leu	Leu
	195						200					205			
Gly	Leu	Lys	Gly	Glu	Leu	Lys	Ile	Ala	Asp	Phe	Gly	Trp	Ser	Val	His
	210					215					220				
Ala	Pro	Ser	Leu	Arg	Arg	Lys	Thr	Met	Cys	Gly	Thr	Leu	Asp	Tyr	Leu
225					230					235					240
Pro	Pro	Glu	Met	Ile	Glu	Gly	Arg	Met	His	Asn	Glu	Lys	Val	Asp	Leu
			245						250					255	
Trp	Cys	Ile	Gly	Val	Leu	Cys	Tyr	Glu	Leu	Leu	Val	Gly	Asn	Pro	Pro
	260							265					270		
Phe	Glu	Ser	Ala	Ser	His	Asn	Glu	Thr	Tyr	Arg	Arg	Ile	Val	Lys	Val
	275						280					285			
Asp	Leu	Lys	Phe	Pro	Ala	Ser	Val	Pro	Thr	Gly	Ala	Gln	Asp	Leu	Ile
	290					295					300				
Ser	Lys	Leu	Leu	Arg	His	Asn	Pro	Ser	Glu	Arg	Leu	Pro	Leu	Ala	Gln
305					310					315					320
Val	Ser	Ala	His	Pro	Trp	Val	Arg	Ala	Asn	Ser	Arg	Arg	Val	Leu	Pro
			325						330					335	
Pro	Ser	Ala	Leu	Gln	Ser	Val	Ala								
			340												

<210> 215

<211> 1421

<212> DNA

<213> Homo sapiens

<400> 215

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agctgcatta acctgcccac tgtgctgccc ggctccccc gcaagaccgg ggggcagatc 120
caggtgattc tcgggccgat gttctcagga aaaagcacag agttgatgag acgcgtccgt 180
cgcttcacaga ttgctcagta caagtgcctg gtgatcaagt atgccaaaga cactcgctac 240
agcagcagct tctgcacaca tgaccggaac accatggagg cgctgccgc ctgcctgctc 300
cgagacgtgg cccaggaggc cctgggcgtg gctgtcatag gcatcgacga ggggcagt 360
ttccctgaca tcatggagtt ctgcgaggcc atggccaacg ccgggaagac cgtaattgtg 420
gctgcactgg atgggacctt ccagagggaag ccatttgggg ccatcctgaa cctggtgccg 480
ctggccgaga gcgtggtgaa gctgacggcg gtgtgcatgg agtgcttccg ggaagccgcc 540
tataccaaga ggctcggcac agagaaggag gtcgaggtga ttgggggagc agacaagtac 600

```

```

cactccgtgt gtcggctctg ctacttcaag aaggcctcag gccagcctgc cgggcccggac 660
aacaagaga actgcccagt gccaggaaag ccaggggaag ccgtggctgc caggaagctc 720
tttggccac agcagattct gcaatgcagc cctgccaaact gagggacctg caagggccgc 780
ccgctccctt cctgccactg cgcctactg gacgctgcc tgcatgctgc ccagccactc 840
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tgtgtggctg cccacactgc cgcctgctcc ctctctctct acccactggg ctgcttaaag 960
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cccttcctac ctctggtgat ggtttccaca ggaacaacag catctttcac caagatgggt 1320
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```

<210> 216

<211> 234

<212> PRT

<213> Homo sapiens

<400> 216

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Met Ser Cys Ile Asn Leu Pro Thr Val Leu Pro Gly Ser Pro Ser Lys
 1           5           10           15
Thr Arg Gly Gln Ile Gln Val Ile Leu Gly Pro Met Phe Ser Gly Lys
          20          25          30
Ser Thr Glu Leu Met Arg Arg Val Arg Arg Phe Gln Ile Ala Gln Tyr
      35          40          45
Lys Cys Leu Val Ile Lys Tyr Ala Lys Asp Thr Arg Tyr Ser Ser Ser
 50          55          60
Phe Cys Thr His Asp Arg Asn Thr Met Glu Ala Leu Pro Ala Cys Leu
65          70          75          80
Leu Arg Asp Val Ala Gln Glu Ala Leu Gly Val Ala Val Ile Gly Ile
      85          90          95
Asp Glu Gly Gln Phe Phe Pro Asp Ile Met Glu Phe Cys Glu Ala Met
      100         105         110
Ala Asn Ala Gly Lys Thr Val Ile Val Ala Ala Leu Asp Gly Thr Phe
      115         120         125
Gln Arg Lys Pro Phe Gly Ala Ile Leu Asn Leu Val Pro Leu Ala Glu
      130         135         140
Ser Val Val Lys Leu Thr Ala Val Cys Met Glu Cys Phe Arg Glu Ala
145         150         155         160
Ala Tyr Thr Lys Arg Leu Gly Thr Glu Lys Glu Val Glu Val Ile Gly
      165         170         175
Gly Ala Asp Lys Tyr His Ser Val Cys Arg Leu Cys Tyr Phe Lys Lys
      180         185         190
Ala Ser Gly Gln Pro Ala Gly Pro Asp Asn Lys Glu Asn Cys Pro Val
      195         200         205
Pro Gly Lys Pro Gly Glu Ala Val Ala Ala Arg Lys Leu Phe Ala Pro
      210         215         220
Gln Gln Ile Leu Gln Cys Ser Pro Ala Asn
225         230

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<210> 217

<211> 2307

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 1691, 1698, 1705, 1708, 1709, 1713, 1717, 1720, 1724, 1728,
1733, 1741, 1746, 1748, 1755, 1770, 1774, 1791, 1802, 1821,
1838, 1856, 1859, 1864, 1908, 1959, 1997, 2012, 2038, 2143

<223> n = A,T,C or G

<400> 217

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cctgccctgc actcgggcct cctccagcca gtgctgacca gggacttctg acctgctggc 180
cagccaggac ctgtgtgggg aggcctcctt gctgccttgg ggtgacaatc tcagctccag 240
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cagaaagggtg gggatcccca tcatcatagc actactgagc ctggcgagta tcatcattgt 420
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ggagcactgt gtcaagagct tccccgaagg gcctgcagtg gcagtccgcc tctccaagga 600
ccgatccaca ctgcagggtg tggactcggc cacagggaac tggttctctg cctgtttcga 660
caacttcaca gaagctctcg ctgagacagc ctgtaggcag atgggctaca gcagcaaacc 720
cactttcaga gctgtggaga ttggcccaga ccaggatctg gatgttgttg aaatcacaga 780
aaacagccag gagcttcgca tgcggaactc aagtgggccc tgtctctcag gctccctggt 840
ctccctgcac tgtcttgccct gtgggaagag cctgaagacc ccccggtgtg tgggtgggga 900
ggaggcctct gtggattctt ggccttggca ggtcagcatc cagtacgaca aacagcacgt 960
ctgtggaggg agcatcctgg accccactg ggtcctcagc gcagcccact gcttcaggaa 1020
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ctgcgggggc ccgagcacc caggagtata caccaaggtc tcagcctatc tcaactggat 1560
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gccnactga acaagggtctc aggggtattg ctaagccaag aaggaaacntt tcccacacta 1920
ctgaatggaa gcaggctgtc ttgtaaaagc ccagatcanc tgtgggctgg agaggagaag 1980
gaaagggtct gcgcccangcc ctgtccgtct tncaccatc cccaagccta ctagagcnaa 2040
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gttgtcattg ttattacagc tatggccact attattaaag agnctgtgta acatcaaaaa 2160
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa ataaataaaa aaaaactcga gggggggccc 2220
ggtacccaat tcgccttata gtgagtcgta ttacaattca ctggccgtcg ttttacaacg 2280
tcgtgactgg gaaaaccctg gcgttac 2307

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<210> 218

<211> 428

<212> PRT

<213> Homo sapiens

<400> 218

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Met Leu Gln Asp Pro Asp Ser Asp Gln Pro Leu Asn Ser Leu Asp Val
 1             5             10            15
Lys Pro Leu Arg Lys Pro Arg Ile Pro Met Glu Thr Phe Arg Lys Val
                20            25            30
Gly Ile Pro Ile Ile Ile Ala Leu Leu Ser Leu Ala Ser Ile Ile Ile
          35             40             45

```

Val Val Val Leu Ile Lys Val Ile Leu Asp Lys Tyr Tyr Phe Leu Cys
 50 55 60
 Gly Gln Pro Leu His Phe Ile Pro Arg Lys Gln Leu Cys Asp Gly Glu
 65 70 75 80
 Leu Asp Cys Pro Leu Gly Glu Asp Glu Glu His Cys Val Lys Ser Phe
 85 90 95
 Pro Glu Gly Pro Ala Val Ala Val Arg Leu Ser Lys Asp Arg Ser Thr
 100 105 110
 Leu Gln Val Leu Asp Ser Ala Thr Gly Asn Trp Phe Ser Ala Cys Phe
 115 120 125
 Asp Asn Phe Thr Glu Ala Leu Ala Glu Thr Ala Cys Arg Gln Met Gly
 130 135 140
 Tyr Ser Ser Lys Pro Thr Phe Arg Ala Val Glu Ile Gly Pro Asp Gln
 145 150 155 160
 Asp Leu Asp Val Val Glu Ile Thr Glu Asn Ser Gln Glu Leu Arg Met
 165 170 175
 Arg Asn Ser Ser Gly Pro Cys Leu Ser Gly Ser Leu Val Ser Leu His
 180 185 190
 Cys Leu Ala Cys Gly Lys Ser Leu Lys Thr Pro Arg Val Val Gly Gly
 195 200 205
 Glu Glu Ala Ser Val Asp Ser Trp Pro Trp Gln Val Ser Ile Gln Tyr
 210 215 220
 Asp Lys Gln His Val Cys Gly Gly Ser Ile Leu Asp Pro His Trp Val
 225 230 235 240
 Leu Thr Ala Ala His Cys Phe Arg Lys His Thr Asp Val Phe Asn Trp
 245 250 255
 Lys Val Arg Ala Gly Ser Asp Lys Leu Gly Ser Phe Pro Ser Leu Ala
 260 265 270
 Val Ala Lys Ile Ile Ile Ile Glu Phe Asn Pro Met Tyr Pro Lys Asp
 275 280 285
 Asn Asp Ile Ala Leu Met Lys Leu Gln Phe Pro Leu Thr Phe Ser Gly
 290 295 300
 Thr Val Arg Pro Ile Cys Leu Pro Phe Phe Asp Glu Glu Leu Thr Pro
 305 310 315 320
 Ala Thr Pro Leu Trp Ile Ile Gly Trp Gly Phe Thr Lys Gln Asn Gly
 325 330 335
 Gly Lys Met Ser Asp Ile Leu Leu Gln Ala Ser Val Gln Val Ile Asp
 340 345 350
 Ser Thr Arg Cys Asn Ala Asp Asp Ala Tyr Gln Gly Glu Val Thr Glu
 355 360 365
 Lys Met Met Cys Ala Gly Ile Pro Glu Gly Gly Val Asp Thr Cys Gln
 370 375 380
 Gly Asp Ser Gly Gly Pro Leu Met Tyr Gln Ser Asp Gln Trp His Val
 385 390 395 400
 Val Gly Ile Val Ser Trp Gly Tyr Gly Cys Gly Gly Pro Ser Thr Pro
 405 410 415
 Gly Val Tyr Thr Lys Val Ser Ala Tyr Leu Asn Trp
 420 425

<210> 219

<211> 556

<212> DNA

<213> Homo sapiens

<400> 219

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 gcttttcctc cgcaaccatg tctgacaaac ccgatatggc tgagatcgag aaattcgata 120
 agtcgaaact gaagaagaca gagacgcaag agaaaaatcc actgccttcc aaagaaacga 180

```

ttgaacagga gaagcaagca ggcgaatcgt aatgaggcgt ggcgcgccaa tatgcaactgt 240
acattccaca agcattgcct tcttattttta cttctttttag ctgtttaact ttgtaagatg 300
caaagagggt ggatcaagtt taaatgactg tgctgcccct ttcacatcaa agaactactg 360
acaacgaagg ccgcgctgcc tttcccatct gtctatctat ctggctggca gggaaggaaa 420
gaacttgcat gttggtgaag gaagaagtgg ggtggaagaa gtgggggtggg acgacagtga 480
aatctagagt aaaaccaagc tggcccaagt gtcctgcagg ctgtaatgca gtttaatcag 540
agtgccattt tttttt

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<210> 220

<211> 44

<212> PRT

<213> Homo sapiens

<400> 220

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Met Ser Asp Lys Pro Asp Met Ala Glu Ile Glu Lys Phe Asp Lys Ser
 1             5             10             15
Lys Leu Lys Lys Thr Glu Thr Gln Glu Lys Asn Pro Leu Pro Ser Lys
      20             25             30
Glu Thr Ile Glu Gln Glu Lys Gln Ala Gly Glu Ser
      35             40

```

<210> 221

<211> 4792

<212> DNA

<213> Homo sapiens

<400> 221

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tctgttgaaa gaatctatca aaagaaaaca caattggaac atatttttgc cgcgccagac 180
acctacattg gttctgtgga attagtgacc cagcaaatgt gggtttacga tgaagatggt 240
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ctagttaatg ctgcggacaa caaacaaagg gacccaaaaa tgtcttgat tagagtcaca 360
attgatccgg aaaacaattt aattagtata tggataatg gaaaagggtat tctgttggt 420
gaacacaaag ttgaaaagat gtatgtccca gctctcatat ttggacagct cctaacttct 480
agtaactatg atgatgatga aaagaaagtg acaggtggtc gaaatggcta tggagccaaa 540
ttgtgtaaca tattcagtag caaatttact gtggaacag ccagtagaga atacaagaaa 600
atgttcaaac agacatggat ggataatatg ggaagagctg gtgagatgga actcaagccc 660
ttcaatggag aagattatac atgtatcacc tttcagcctg atttgtctaa gtttaaaatg 720
caaagcctgg acaaagatat tggtgcacta atggtcagaa gagcatatga tattgctgga 780
tccaccaaag atgtcaaagt ctttcttaat ggaaataaac tgccagtaaa aggatttcgt 840
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atacatgaac aagtaaacca caggtgggaa gtgtgtttta ctatgagtga aaaaggcttt 960
cagcaaatta gctttgtcaa cagcattgct acatccaagg gtggcagaca tggtgattat 1020
gtagctgatac agattgtgac taaacttggt gatgttgta agaagaagaa caagggtggg 1080
gttgacagtaa aagcacatca ggtgaaaaat cacatgtgga tttttgtaaa tgccttaatt 1140
gaaaacccaa cctttgactc tcagacaaaa gaaaacatga ctttacaacc caagagcttt 1200
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<210> 222

<211> 1531

<212> PRT

<213> Homo sapiens

<400> 222

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Ala	His	Gln	Val	Lys	Asn	His	Met	Trp	Ile	Phe	Val	Asn	Ala	Leu	Ile	
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Glu	Asn	Pro	Thr	Phe	Asp	Ser	Gln	Thr	Lys	Glu	Asn	Met	Thr	Leu	Gln	
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Val	Ala	Ile	Leu	Asn	Ser	Thr	Thr	Ile	Glu	Ile	Ser	Glu	Leu	Pro	Val
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His	Thr	Asp	Thr	Thr	Val	Lys	Phe	Val	Val	Lys	Met	Thr	Glu	Glu	Lys

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 1475 1480 1485
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<211> 1111

<212> DNA

<213> Homo sapiens

<400> 223

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<210> 224

<211> 284

<212> PRT

<213> Homo sapiens

<400> 224

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  35          40          45
Lys Leu Lys Gly Thr Glu Asp Glu Leu Asp Lys Tyr Ser Glu Ala Leu
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Lys Asp Ala Gln Glu Lys Leu Glu Leu Ala Glu Lys Lys Ala Thr Asp
  65          70          75          80
Ala Glu Ala Asp Val Ala Ser Leu Asn Arg Arg Ile Gln Leu Val Glu
  85          90          95
Glu Glu Leu Asp Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys

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Lys Tyr Glu Glu Val Ala Arg Lys Leu Val Ile Ile Glu Ser Asp Leu		
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Leu Glu Glu Glu Leu Lys Thr Val Thr Asn Asn Leu Lys Ser Leu Glu		
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<211> 501

<212> DNA

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<213> Homo sapiens

<400> 226

Met Val Lys Gln Ile Glu Ser Lys Thr Ala Phe Gln Glu Ala Leu Asp	
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Ala Ala Gly Asp Lys Leu Val Val Val Asp Phe Ser Ala Thr Trp Cys	
20	30
Gly Pro Cys Lys Met Ile Asn Pro Phe Phe His Ser Leu Ser Glu Lys	
35	45
Tyr Ser Asn Val Ile Phe Leu Glu Val Asp Val Asp Asp Cys Gln Asp	
50	60
Val Ala Ser Glu Cys Glu Val Lys Cys Thr Pro Thr Phe Gln Phe Phe	
65	80
Lys Lys Gly Gln Lys Val Gly Glu Phe Ser Gly Ala Asn Lys Glu Lys	
85	95

Leu Glu Ala Thr Ile Asn Glu Leu Val
100 105

<210> 227
<211> 783
<212> DNA
<213> Homo sapiens

<400> 227
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ccgggggtccg gtgggcaaaa ggctacagca ggagctgatg accctcatga tgtctggcga 180
taaagggtatt tctgccttcc ctgaatcaga caaccttttc aaatgggtag ggaccatcca 240
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aaa 783

<210> 228
<211> 179
<212> PRT
<213> Homo sapiens

<400> 228
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Lys Arg Leu Gln Gln Glu Leu Met Thr Leu Met Met Ser Gly Asp Lys
35 40 45
Gly Ile Ser Ala Phe Pro Glu Ser Asp Asn Leu Phe Lys Trp Val Gly
50 55 60
Thr Ile His Gly Ala Ala Gly Thr Val Tyr Glu Asp Leu Arg Tyr Lys
65 70 75 80
Leu Ser Leu Glu Phe Pro Ser Gly Tyr Pro Tyr Asn Ala Pro Thr Val
85 90 95
Lys Phe Leu Thr Pro Cys Tyr His Pro Asn Val Asp Thr Gln Gly Asn
100 105 110
Ile Cys Leu Asp Ile Leu Lys Glu Lys Trp Ser Ala Leu Tyr Asp Val
115 120 125
Arg Thr Ile Leu Leu Ser Ile Gln Ser Leu Leu Gly Glu Pro Asn Ile
130 135 140
Asp Ser Pro Leu Asn Thr His Ala Ala Glu Leu Trp Lys Asn Pro Thr
145 150 155 160
Ala Phe Lys Lys Tyr Leu Gln Glu Thr Tyr Ser Lys Gln Val Thr Ser
165 170 175
Gln Glu Pro

<210> 229
<211> 777

<212> DNA

<213> Homo sapiens

<400> 229

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<210> 230

<211> 165

<212> PRT

<213> Homo sapiens

<400> 230

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Met Ala Pro Asn Ala Ser Cys Leu Cys Val His Val Arg Ser Glu Glu
1          5          10          15
Trp Asp Leu Met Thr Phe Asp Ala Asn Pro Tyr Asp Ser Val Lys Lys
20        25        30
Ile Lys Glu His Val Arg Ser Lys Thr Lys Val Pro Val Gln Asp Gln
35        40        45
Val Leu Leu Leu Gly Ser Lys Ile Leu Lys Pro Arg Arg Ser Leu Ser
50        55        60
Ser Tyr Gly Ile Asp Lys Glu Lys Thr Ile His Leu Thr Leu Lys Val
65        70        75        80
Val Lys Pro Ser Asp Glu Glu Leu Pro Leu Phe Leu Val Glu Ser Gly
85        90        95
Asp Glu Ala Lys Arg His Leu Leu Gln Val Arg Arg Ser Ser Ser Val
100       105       110
Ala Gln Val Lys Ala Met Ile Glu Thr Lys Thr Gly Ile Ile Pro Glu
115       120       125
Thr Gln Ile Val Thr Cys Asn Gly Lys Arg Leu Glu Asp Gly Lys Met
130       135       140
Met Ala Asp Tyr Gly Ile Arg Lys Gly Asn Leu Leu Phe Leu Ala Ser
145       150       155       160
Tyr Cys Ile Gly Gly
165

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<210> 231

<211> 4797

<212> DNA

<213> Homo sapiens

<400> 231

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<210> 232

<211> 433

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> 433

<223> Xaa = Any Amino Acid

<400> 232

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Met Pro His Ser Pro Leu Ile Ser Ile Pro His Val Trp Cys His Pro
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Glu Glu Glu Glu Arg Met His Asp Glu Leu Leu Gln Ala Val Ser Lys
20          25          30
Gly Pro Val Met Phe Arg Asp Val Ser Ile Asp Phe Ser Gln Glu Glu
35          40          45
Trp Glu Cys Leu Asp Ala Asp Gln Met Asn Leu Tyr Lys Glu Val Met
50          55          60
Leu Glu Asn Phe Ser Asn Leu Val Ser Val Gly Leu Ser Asn Ser Lys
65          70          75          80
Pro Ala Val Ile Ser Leu Leu Glu Gln Gly Lys Glu Pro Trp Met Val
85          90          95
Asp Arg Glu Leu Thr Arg Gly Leu Cys Ser Asp Leu Glu Ser Met Cys
100          105          110
Glu Thr Lys Ile Leu Ser Leu Lys Lys Arg His Phe Ser Gln Val Ile
115          120          125
Ile Thr Arg Glu Asp Met Ser Thr Phe Ile Gln Pro Thr Phe Leu Ile
130          135          140
Pro Pro Gln Lys Thr Met Ser Glu Glu Lys Pro Trp Glu Cys Lys Ile
145          150          155          160
Cys Gly Lys Thr Phe Asn Gln Asn Ser Gln Phe Ile Gln His Gln Arg
165          170          175
Ile His Phe Gly Glu Lys His Tyr Glu Ser Lys Glu Tyr Gly Lys Ser
180          185          190
Phe Ser Arg Gly Ser Leu Val Thr Arg His Gln Arg Ile His Thr Gly
195          200          205
Lys Lys Pro Tyr Glu Cys Lys Glu Cys Gly Lys Ala Phe Ser Cys Ser
210          215          220
Ser Tyr Phe Ser Gln His Gln Arg Ile His Thr Gly Glu Lys Pro Tyr
225          230          235          240
Glu Cys Lys Glu Cys Gly Lys Ala Phe Lys Tyr Cys Ser Asn Leu Asn

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290

[illegible]

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<210> 233
<211> 1860
<212> DNA
<213> Homo sapiens
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<210> 234

<211> 501

<212> PRT

<213> Homo sapiens

<400> 234

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      20           25           30
Pro Arg Arg Pro Ala Ser Thr Ala Gly Ser Ala Pro Phe Pro Glu Gly
      35           40           45
Trp Met Met Gly Cys Phe Ala Leu Gln Thr Val Asp Thr Glu Leu Thr
      50           55           60
Ala Asp Ser Val Glu Trp Cys Pro Leu Gln Gly Cys Arg His Leu Leu
      65           70           75           80
Ala Cys Gly Thr Tyr Gln Leu Arg Arg Pro Glu Asp Arg Pro Ala Gly
      85           90           95
Pro Gln Asn Lys Gly Gly Met Glu Val Lys Glu Pro Gln Val Arg Leu
      100          105          110
Gly Arg Leu Phe Leu Tyr Ser Phe Asn Asp Asn Asn Ser Ile His Pro
      115          120          125
Leu Val Glu Val Gln Arg Lys Asp Thr Ser Ala Ile Leu Asp Met Lys
      130          135          140
Trp Cys His Ile Pro Val Ala Gly His Ala Leu Leu Gly Leu Ala Asp
      145          150          155          160
Ala Ser Gly Ser Ile Gln Leu Leu Arg Leu Val Glu Ser Glu Lys Ser
      165          170          175
His Val Leu Glu Pro Leu Ser Ser Leu Ala Leu Glu Glu Gln Cys Leu
      180          185          190
Ala Leu Ser Leu Asp Trp Ser Thr Gly Lys Thr Gly Arg Ala Gly Asp
      195          200          205
Gln Pro Leu Lys Ile Ile Ser Ser Asp Ser Thr Gly Gln Leu His Leu
      210          215          220
Leu Met Val Asn Glu Thr Arg Pro Arg Leu Gln Lys Val Ala Ser Trp
      225          230          235          240
Gln Ala His Gln Phe Glu Ala Trp Ile Ala Ala Phe Asn Tyr Trp His
      245          250          255
Pro Glu Ile Val Tyr Ser Gly Gly Asp Asp Gly Leu Leu Arg Gly Trp
      260          265          270
Asp Thr Arg Val Pro Gly Lys Phe Leu Phe Thr Ser Lys Arg His Thr
      275          280          285
Met Gly Val Cys Ser Ile Gln Ser Ser Pro His Arg Glu His Ile Leu
      290          295          300
Ala Thr Gly Ser Tyr Asp Glu His Ile Leu Leu Trp Asp Thr Arg Asn
      305          310          315          320
Met Lys Gln Pro Leu Ala Asp Thr Pro Val Gln Gly Gly Val Trp Arg
      325          330          335
Ile Lys Trp His Pro Phe His His His Leu Leu Leu Ala Ala Cys Met
      340          345          350
His Ser Gly Phe Lys Ile Leu Asn Cys Gln Lys Ala Met Glu Glu Arg
      355          360          365

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Gln Glu Ala Thr Val Leu Thr Ser His Thr Leu Pro Asp Ser Leu Val
 370 375 380
 Tyr Gly Ala Asp Trp Ser Trp Leu Leu Phe Arg Ser Leu Gln Arg Ala
 385 390 395 400
 Pro Ser Trp Ser Phe Pro Ser Asn Leu Gly Thr Lys Thr Ala Asp Leu
 405 410 415
 Lys Gly Ala Ser Glu Leu Pro Thr Pro Cys His Glu Cys Arg Glu Asp
 420 425 430
 Asn Asp Gly Glu Gly His Ala Arg Pro Gln Ser Gly Met Lys Pro Leu
 435 440 445
 Thr Glu Gly Met Arg Lys Asn Gly Thr Trp Leu Gln Ala Thr Ala Ala
 450 455 460
 Thr Thr Arg Asp Cys Gly Val Asn Pro Glu Glu Ala Asp Ser Ala Phe
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 Glu Trp Glu Gly Asn
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<210> 235

<211> 1614

<212> DNA

<213> Homo sapiens

<400> 235

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<210> 236

<211> 247

<212> PRT

<213> Homo sapiens

<400> 236

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Thr Ile Met Lys Ala Arg Leu Lys Gly Ala Gln Thr Gly Arg Asn Leu
      20           25           30
Leu Lys Lys Lys Ser Asp Ala Leu Thr Leu Arg Phe Arg Gln Ile Leu
      35           40           45
Lys Lys Ile Ile Glu Thr Lys Met Leu Met Gly Glu Val Met Arg Glu
      50           55           60
Ala Ala Phe Ser Leu Ala Glu Ala Lys Phe Thr Ala Gly Asp Phe Ser
      65           70           75           80
Thr Thr Val Ile Gln Asn Val Asn Lys Ala Gln Val Lys Ile Arg Ala
      85           90           95
Lys Lys Asp Asn Val Ala Gly Val Thr Leu Pro Val Phe Glu His Tyr
      100          105          110
His Glu Gly Thr Asp Ser Tyr Glu Leu Thr Gly Leu Ala Arg Gly Gly
      115          120          125
Glu Gln Leu Ala Lys Leu Lys Arg Asn Tyr Ala Lys Ala Val Glu Leu
      130          135          140
Leu Val Glu Leu Ala Ser Leu Gln Thr Ser Phe Val Thr Leu Asp Glu
      145          150          155          160
Ala Ile Lys Ile Thr Asn Arg Arg Val Asn Ala Ile Glu His Val Ile
      165          170          175
Ile Pro Arg Ile Glu Arg Thr Leu Ala Tyr Ile Ile Thr Glu Leu Asp
      180          185          190
Glu Arg Glu Arg Glu Glu Phe Tyr Arg Leu Lys Lys Ile Gln Glu Lys
      195          200          205
Lys Lys Ile Leu Lys Glu Lys Ser Glu Lys Asp Leu Glu Gln Arg Arg
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<210> 237

<211> 1658

<212> DNA

<213> Homo sapiens

<400> 237

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<210> 238

<211> 277

<212> PRT

<213> Homo sapiens

<400> 238

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  20          25          30
Glu Leu Pro Ala Lys Ile Leu Val Glu Phe Val Val Asp Ser Gln Lys
  45          40          45
Lys Asp Lys Leu Leu Cys Ser Gln Leu Gln Val Ala Asp Phe Leu Gln
  50          55          60
Asn Ile Leu Ala Gln Glu Asp Thr Ala Lys Gly Leu Asp Pro Leu Ala
  65          70          75          80
Ser Glu Asp Thr Ser Arg Gln Lys Ala Ile Ala Ala Lys Glu Gln Trp
  85          90          95
Lys Glu Leu Lys Ala Thr Tyr Arg Glu His Val Glu Ala Ile Lys Ile
  100         105         110
Gly Leu Thr Lys Ala Leu Thr Gln Met Glu Glu Ala Gln Arg Lys Arg
  115         120         125
Thr Gln Leu Arg Glu Ala Phe Glu Gln Leu Gln Ala Lys Lys Gln Met
  130         135         140
Ala Met Glu Lys Arg Arg Ala Val Gln Asn Gln Trp Gln Leu Gln Gln
  145         150         155         160
Glu Lys His Leu Gln His Leu Ala Glu Val Ser Ala Glu Val Arg Glu
  165         170         175
Arg Lys Thr Gly Thr Gln Gln Glu Leu Asp Gly Val Phe Gln Lys Leu
  180         185         190
Gly Asn Leu Lys Gln Gln Ala Glu Gln Glu Arg Asp Lys Leu Gln Arg
  195         200         205
Tyr Gln Thr Phe Leu Gln Leu Leu Tyr Thr Leu Gln Gly Lys Leu Leu
  210         215         220
Phe Pro Glu Ala Glu Ala Glu Ala Glu Asn Leu Pro Asp Asp Lys Pro
  225         230         235         240
Gln Gln Pro Thr Arg Pro Gln Glu Gln Ser Thr Gly Asp Thr Met Gly
  245         250         255
Arg Asp Pro Gly Val Ser Phe Lys Ala Val Gly Leu Gln Pro Ala Gly
  260         265         270
Asp Val Asn Leu Pro
  275

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